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VOLUME 1 APRIL, 1928 NUMBER 10

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ANNALS OF INTERNAL MEDICINE

PUBLISHED BY

The American College of Physicians

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Issued Monthly

ANN ARBOR, MICHIGAN

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PATHOLOGY DEPARTMENT

ANNALS OF INTERNAL MEDICINE

OFFICIAL PERIODICAL OF THE AMERICAN COLLEGE OF PHYSICIANS

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DEPARTMENT OF REVIEWS

The Journal will make an especial feature of the review of monographs and books bearing upon the field of Internal Medicine. Authors and publishers wishing to subject such material for the purposes of review should send it to the editor. While obviously impossible to make extended reviews of all material, an acknowledgment of all matter sent will be made in the department of reviews.

Editor

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Experimental Study of Acquired Resistance of the Rabbit's Renal Epithelium to Uranyl Nitrate

By Warren C. Hunter, M.A. M.D., *Portland, Oregon**†

THE ability of renal cells to regenerate after injury is scarcely mentioned in most textbooks of medicine. That these cells must have a remarkable regenerative power is best seen in the kidneys of individuals recovering from scarlet fever in which later examination will often reveal no evidence of previous damage, indicating complete restitution of damaged epithelium. The same thing occurs in the varying degrees of nephrosis accompanying many acute infections. It is also true that some cellular regeneration takes place after injury by metallic salts or other chemicals which act on the kidney.

A question which has received even less attention than regeneration is the intrinsic nature of the new epithelial cells. Are these in all respects identical with the original epithelium of the same location? Is it possible that new cells, perhaps formed while the injury is still going on, develop a tolerance, increased resistance or even a specific immunity for the substance capable of killing the original epithelium? We are accustomed to think of immunity as a general protective mechanism on the part of the body against subsequent injury by the same agent rather than a reaction of specific cells, yet in recent years there has been an increasing tendency to regard immunity as a local cellular phenomenon. French investigators, particularly Besredka, (1)

(1) Besredka, Alexandre. Local Immunization. Williams and Wilkins Co., Baltimore, 1927.

have been especially active in this respect, while in this country the work of Rivers and Tillett, (2) Bowen (3) Mallory and Marble (4) and Gay (5) are worthy of mention.

(2) Rivers, T.M. and Tillett, W.S., Local passive immunity in skin of rabbits to infection with (1) a filterable virus and (2) hemolytic streptococci. J. Exper. Med. 41: p. 185-194, 1925.

(3) Bowen, J. A., Production of local immunity by means of diphtheria toxin. J. Infect. Diseases 36: p. 501-507, 1925.

(4) Mallory, T. B. and Marble, A., Local immunization of rabbits to cutaneous infection with staphylococcus aureus, J. Exper. Med. 42: p. 465-472, 1925.

(5) Gay, F. P. Local or tissue immunity. Arch. Path. and Lab. Med. 1: p. 590-604, 1926.

As dealing with what is probably a somewhat similar local immunity re-

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action may be mentioned the recent work of Weller (6) who has been able

(6) Weller, C. V., Tolerance in respect to the meningocerebral manifestations of acute and subacute lead poisoning. Arch. Int. Med. 39: p. 45-59, 1927.

to demonstrate in guinea pigs a tolerance to the meningocerebral manifestations of lead poisoning.

The question of immunity of renal epithelium is of the greatest importance in relation to our conception of tubular nephritis. In this connection Aschoff (7) states: "According to Metchnikoff, Adami and others, an essential characteristic of the inflammatory process consists in the fact that it essentially represents a defense mechanism. In the case of infections, this defense mechanism is, as a rule, associated with a process of immunization. If a tissue or a cell develops an increased resistance against a bacterial or other poison, it is safe to assume that these particular cells have taken part in the process of defense. I am therefore prepared to express the belief that parenchymatous or tubular nephritis represents a reaction of the kidney to some poison, and that in the case of this reaction the epithelium itself takes part in the chemical transformation of the poison and in its detoxication. The kidneys of an animal which has survived a parenchymatous, i. e., a tubular, nephritis, produced by a poison, must show an increased resistance of the epithelium to further administrations of the same poison" (p. 355).

(7) Aschoff, L., Lectures on Pathology, chap. xiv, p. 340-358, Paul Hoeber, New York, 1924 .

(1.) See also Gay, Frederick P., Local resistance and local immunity to bacteria. Physiol Rev. 4: p. 191, 1924.

The one previous experimental investigation concerned with immunization of renal epithelium is that of Gil y Gil (8) but before discussing this work it is necessary to review briefly the literature on experimental chronic nephritis.

(8) Gil y Gil, Carlos., Die Immunität im Nierenepithelgewebe, Beiträge zur path. Anat., 72: p. 621-653, 1924.

Review of Literature.

The literature on experimental nephritis produced by various mechanical injuries and many nephrotoxic substances, particularly the salts of heavy metals and numerous organic toxins and poisons is voluminous. Most investigators have been concerned almost entirely with the nature of the pathological lesion or functional alterations, and few have noted or given more than passing mention to regeneration of epithelium. Fewer still have concerned themselves with the problem of immunity.

With uranium nitrate most workers have limited their field to functional studies, using rather large doses and producing such extensive kidney damage that the animals died before any or but very little regeneration was possible. Such investigations, although valuable for the purpose intended, offer little of value to the present study.

Chittenden and Lambert (9) were the first to demonstrate the nephrotoxic action of uranium salts. Although their problem was physiological and no mention of tolerance is made

(9) Chittenden, R. H. and Lambert, A., Untersuchungen über die physiologische Wirkung der Uransalze. Ztschr. f. Biologie, 25: p. 512, 1889.

the results obtained in one dog suggest this possibility since after a period during which no uranium was given nearly ten times the original dose was required to produce the same evidences of intoxication.

At one time uranium was used by some physicians in the treatment of diabetes mellitus and several reports in which tolerance is mentioned or suggested have been found. West (10) found that larger doses were necessary

(10) West, Samuel, Brit. M. J. 2: p. 467-472, 1895. Uranium nitrate in diabetes mellitus.

to obtain the same effect in patients in whom the drug had been stopped for a time, perhaps indicating that some degree of tolerance had been acquired. Burton (11) increased the daily dos-

(11) Burton, A., A case of diabetes treated by uranium nitrate, Brit. M. J. 2: p. 847, 1896.

age of uranium from 3 to 15 grains and noted that when this amount was discontinued he could later start with the quantity last given. Duncan (12) was likewise able to increase the dostage in diabetics. Bond (13) gave a

(12) Duncan, E., Uranium nitrate in diabetes, Brit. M. J. 2: p. 1044, 1897.

(13) Bond, C. H., Uranium nitrate: its value in the control of glycosuria, Practitioner, p. 257, 1898.

diabetic patient as much as 90 grains of uranium nitrate daily for a year without harmful effect. Tylecote (14) treated a diabetic whom he believed

(14) Tylecote, F. E., The pharmacology and therapeutics of uranium. Medical Chronicle, 40: p. 379, 1904.

demonstrated tolerance for uranium. The initial dose of 3 grains daily was increased gradually to 5 grains but discontinued because of constipation and a temporary cloud of albumin. He later began at the full previous amount without ill effect. The only recent report of this nature is that of Wilcox (15) who states that he has used

(15) Wilcox, R. W., Therapeutics of uranium nitrate, Medical Record, 92: p. 361, 1917.

uranium in some diabetic patients for months or even years without deleterious effect.

As to the lower vertebrates but one reference of tolerance to uranium has been encountered. Denis (16) gave the dog fish (Mustelis canis) as

(16) Denis, W. Note on the tolerance shown by elasmobranch fish toward certain nephrotoxic agents. J. Biol. Chem. 16: p. 395, 1913-1914.

much as 80 milligrams per kilogram body weight without ill effects being shown. Reference to her chart, however, shows that when 106 or more milligrams per kilo was administered the fish died within 1 to 3 days. The doses were neither repeated nor increased and for this reason it appears to the writer that tolerance was not established, at least not in the sense commonly understood.

A number of investigators have succeeded in obtaining more or less chronic renal lesions with uranium nitrate. Siegel (17) is apparently the

(17) Siegel, W., Ein Stoffwechselversuch bei Urannephritis am Hunde. Ztschr. f. exper. Path. u. Therap. 4: p. 561-575, 1907.

first. In a dog given two small doses of uranium nitrate and killed after thirty days the pathological changes in

the kidney are described as chronic parenchymatous nephritis with interstitial changes. There is no mention of regeneration.

Two years later Dickson (18) made an extensive study of uranium nephritis, producing in guinea pigs lesions closely resembling those seen in subacute and chronic diffuse nephritis in man. A series of subacute attacks were followed by extensive fibrosis of the kidney, in some instances proceeding to the stage of granular atrophy. He did not increase the dosage of uranium nor does he describe cellular regeneration. A second report by Dickson (19) appeared in 1912. In this study guinea pigs, rabbits and dogs were employed in the hope of confirming previous observations and producing the condition among animals of different kinds which would be better suited for secondary experiments. In all animals characteristic and very similar lesions were found. A granular atrophy in which the histological picture was that of an extreme and progressive fibrosis with accompanying changes in the tubules and glomeruli he felt could not be described other than as a true chronic diffuse nephritis. In some rabbits and dogs the initial dose was increased as much as five times without killing the animals but even the largest doses were still within the limit of tolerance for normal animals. In one rabbit Dickson saw "evidence of epithelial regeneration in many tubules."

(18) Dickson, E. C., A report on the experimental production of chronic nephritis in animals by the use of uranium nitrate. Arch. Int. Med. 3: p. 375-410, 1909.

(19) Dickson, E. C., A further report on the production of experimental chronic nephritis by the administration of uranium nitrate. Arch. Int. Med. 9: p. 557-591, 1912.

In rabbits poisoned with uranium nitrate and potassium bichromate Smith (20) saw only patchy round cell infiltration and small areas of fibrosis in the cortex. In the few instances where the doses were increased this was not progressive. Epithelial regeneration or increased resistance of the animals to the poisons is not mentioned.

Suzuki (21) in the course of an exhaustive experimental investigation of renal secretion induced varying degrees of chronic nephritis in guinea pigs by the use of uranium nitrate. In some animals receiving more than one injection the later doses were somewhat larger than at the start. In summary Suzuki calls attention to the fact that the sensitivity of the regenerated epithelium in the presence of repeated uranium poisoning becomes remarkably slight. When death of the animals occurred soon after the last administration of uranium very little injury of the epithelium in the distal and transitional segments of the proximal convoluted tubules (the selective site of injury by uranium) could be made out. Thus Suzuki, although giving

(20) Christian, H. A., Smith, R. M. and Walker, I. C., Experimental cardio-renal disease. Study V. Smith, R. M., Experimental chronic nephritis, Arch. Int. Med., 8: p. 482, 1911.

(21) Suzuki, Tatzuo., Zur Morphologie der Nierensekretion unter physiologischen und pathologischen Bedingungen, Fischer, Jena, 1912.

the matter only passing mention, was the first to recognize the phenomenon of increased cellular resistance to poisons.

Baehr (22) administered small subcutaneous doses of uranium nitrate

(22) Baehr, George, Über experimentelle Glomerulonephritis, Beiträge zur path. Anat. 55: p. 545-574, 1913.

to ten rabbits and in one noted a considerable proliferation of the glomerular capsular epithelium. When very small quantities were injected directly into the renal artery more uniform results were obtained, leading to proliferation of the epithelium of Bowman's membrane, adhesion to the glomerular tufts and epithelial crescent formation. Tubular damage was slight.

An excellent and thorough study of epithelial regeneration and interstitial connective tissue proliferation in the uranium kidney was made by Oliver (23) in 1915.

(23) Oliver, Jean., The histogenesis of chronic uranium nephritis with especial reference to epithelial regeneration. J. Exper. Med., 21: p. 425-451, 1915.

Of the many chemical substances other than uranium nitrate which have been used in attempts to provoke chronic renal lesions only a few need be mentioned.

Petroff (24) using the salts of Hg,

(24) Petroff, Theodor., Ueber die Einwirkung der Metalle auf die Nieren. Inaug. Diss. Würzburg, 1905.

Cu, Zn, Fe, Ag, P. and As., found that when the action was continued for some time there resulted necrosis of the renal epithelium and proliferation of the connective tissue.

Ehrlich (25) and Levaditi (26) by the use of vinyl amine produced defi-

(25) Ehrlich, Ueber die Zusammenhang von Chemischer Constitution und Wirkung. 1898, cited by Dickson, Arch. Int. Med. 3: p. 384, 1909.

(26) Levaditi, Experimentelle Untersuchungen über die Necrose der Nierenpapillae, Arch. internat. de Pharmacod., 8: p. 45, 1901, cited by Dickson, Arch. Int. Med. 3: p. 384, 1909.

nite fibrosis of the kidneys in white mice, secondary to localized hemorrhagic necrosis of the papillae.

Ophüls (27) fed lead carbonate to guinea pigs over periods of two to

(27) Ophüls, W., Experimental chronic nephritis, J. A. M. A. 48: p. 483, 1907.

five months. The lesions, which were very similar in all, consisted in comparatively slight changes in the epithelium of the convoluted tubules and ascending limbs of Henle with some degeneration and desquamation of cells. An active regenerative process in the epithelium was indicated by the occurrence of occasional mitotic figures. Slight interstitial proliferation and small foci of lymphocytes were noted. Lead acetate was administered to dogs in drinking water, and when treated for a sufficient length of time there developed chronic interstitial nephritis, which though not extreme was definite enough to make sure of the process. A few dogs also received potassium bichromate. In a later communication Ophüls (28) expresses the opinion that the lesions in one chromate dog

(28) Ophüls, W. Some interesting points in regard to experimental chronic nephritis. J. Med. Research. 18: p. 497, 1908.

reported in the previous paper (27)

were evidently spontaneous in origin and is doubtful as to the reality of the changes in two others. In the latter communication (28) appears a statement of great interest because it shows that Ophüls recognized the development of tolerance for renal poisons. In connection with one dog in which the dosage was raised quite perceptibly over a period of sixteen months he says: "The experiments so far show, however, quite clearly that after awhile dogs also will tolerate doses without much injury, which at first would have done them serious damage, if not killed them outright" (p. 506).

Recently Frandsen (29) has reported the production of well marked

(29) Frandsen, Johannes, Sur les Néphrites Chroniques Experimentales. Compt. rend. Soc. de biol. 91: p. 413-415, July 11, 1924.

chronic glomerulo-tubular nephritis in rabbits by the intravenous injection of sodium cantharidate. Other rabbits given potassium bichromate intravenously exhibited marked tubular and glomerular atrophy with great increase in interstitial tissue. Frandsen believes the latter type of nephritis remains a purely tubular one for several months, the glomeruli being affected only in the last stages.

Jessen (30) has recently perfected a technique (hypodermoclysis) by

(30) Jessen, Jes., Méthode ayant pour but de provoquer des Néphritis Chroniques chez le Lapin. Compt. rend. Soc. de biol. 91: p. 1111-1113, Nov. 21, 1924, (illus.)

means of which long continued subcutaneous administration of both inorganic and organic substances in very weak concentration can be carried out and which he believes produces more uniform results than are obtainable by the usual modes of administration. By this method Jessen (31) has induced a pure tubular nephritis with potas-

(31) Jessen, Jes., Nye Undersogelser over Kromnefritis, Hospitalstid. 68: p. 921, Oct. 1, 1925.

sium chromate in which after a time there was well developed connective tissue and lymphocytic infiltration in the region of the glomeruli and affected tubules. He (32) has likewise given uranyl acetate to rabbits by the drip

(32) Jessen, Jes., Nye Undersogelser over Urannefritis, Hospitalstid, 68: p. 656, 1925.

method. After three months all animals showed regeneration of epithelium in the third and fourth segments of the proximal convoluted tubules with increase of connective tissue and sometimes marked lymphocytic infiltration about the affected tubules. Bing, Heckscher and Jessen (33) found regeneration of cells in the proximal con-

(33) Bing, H. J., Heckscher, H., and Jessen, J., Studies on the fat-cholesterol contents of the blood in rabbits suffering from an artificial nephritis. Acta path. et microbiol. Scandinav. 2: p. 234, 1925.

voluted tubules, together with slight connective tissue proliferation in a rabbit first given uranyl acetate and later phosphorus by hypodermoclysis. Although uranyl acetate was administered to a number of rabbits over periods of several months the total quantity never exceeded 40 milligrams.

The roentgen ray was employed as a means of provoking chronic nephritis as early as 1905 by Schulz and Hoff-

mann (34) but seems to have been for-

(34) Schulz and Hoffmann, Deutsch, Ztschr. f. Chir. 79: p. 350, 1905.

gotten until recently when Hartman, Bolliger and Doub (35), O'Hare and others (36) have revived its use.

(35) Hartman, F. W., Bolliger, A., and Doub. H. P., Experimental Nephritis produced by Irradiation. Am. J. Med. Sci. 172: p. 487-501, Oct., 1926.

(36) O'Hare, J. P., Altnow, H., Christian, T. D. Jr., Calhoun, A. W. and Sosman, M. C. Chronic Nephritis produced by X-ray. Boston M. and S. J. 194: p. 43-45, 1926.

The first named authors (35) found pathological alterations in all kidney structures, the order of severity being interstitial, vascular, and glomerular while the latter (36) describe extensive connective tissue increase, sclerosis of vessels and atrophy of the tubules. Bell, Clawson and Hartzell (37) have produced glomerulonephritis

(37) Bell, E. T., Clawson, B. J. and Hartzell, T. B., Experimental glomerulonephritis Am. J. Path. 1: p. 247, 1925.

in monkeys by repeated intravenous injections of streptococci.

The foregoing review does not include all experimental work on chronic nephritis. Some references which have little value or merit have been omitted. Full and comprehensive discussions of the older literature on the subject will be found in the works of Lyon (38) and Ophüls (27). More recently Mac-

(38) Lyon, George., Inflammatory changes in the kidney: an experimental study of the action of some toxins and poisons upon the kidney and also upon the spleen. J. Path. and Bact. 9: p. 400-456, 1903.

Nider (39) has fully reviewed the lit-

(39) MacNider, Wm. de B., A Review of Acute Experimental nephritis. Physiol. Rev. 4: p. 595-638, 1924.

erature on acute experimental nephritis.

The only authors who have directly mentioned immunity of renal epithelium are Suzuki (loc. cit.) and Gil y Gil (loc. cit.) Since the latter is the only investigator whose research has been wholly concerned with this problem it becomes necessary, on account of the writer having repeated the work, to discuss Gil y Gil's article somewhat in detail.

Critical Review.

Gil y Gil states that although a number of research workers have shown that unicellular or higher organisms are capable of developing an immunity for certain substances, the site or morphology of this immunity could not be established. It appeared to him that if immunity of definite cells in higher animals is to be demonstrated, poisons having a direct specific action on these cells must be used. Suzuki's experiments had shown that sublimate and uranium nitrate affect only the epithelium of the proximal convoluted tubules and in some dosages only certain segments of these. Thus the thought occurred to Gil y Gil that with repeated administrations of sufficiently small quantities of poisons the renal epithelium might become tolerant to doses larger than the lethal.

Because of the general action which these poisons also have, the author speaks with caution of the manner in which a local immunity is attained. It appeared to him conceivable that in

repeatedly poisoned animals the uranium might no longer pass through the kidney but be assimilated and excreted by other channels. On account of this possibility it seemed necessary to prove whether or not uranium was excreted by immunized and acutely poisoned kidneys.

Immunization with uranium proved more difficult than with sublimate for after too large or too frequently repeated doses the animals refused food, lost weight and often died. A certain number in his series had only one injection to determine the lethal dose, some died during the course of immunization and only a few could be regarded as successfully immunized. The total number of rabbits employed in the experiments was twenty-four.

Study of the kidney following a single injection of uranium demonstrated that the changes vary according to the quantity given and the duration of time after the injection. In two rabbits regarded as the best examples of immunization there was little or no fresh epithelial damage after dosages capable of evoking very pronounced changes in the normal kidney. This was regarded as proof of tolerance on the part of the epithelium of immunized kidneys.

A number of chemical methods were employed in the hope of determining whether the uranium given was excreted through the kidney or was combined with the tubular cell protoplasm or in other organs, particularly the liver. None gave satisfactory results and were accordingly abandoned.

The formation of uranyl ferrocyanide in a uranium-containing solution by reaction with potassium ferrocyanide was taken as a basis for the quantitative estimation of uranium in the urine. Unfortunately the method could not be used if iron was also present and for this reason he was unable to obtain any results with the kidney and liver and only rarely with urine since traces of blood were found to be present in most specimens.

Finally a biological method was tried. Urine from uranium rabbits was collected, sterilized and injected intraperitoneally in mice. Tubular lesions having the same localizations as in the rabbits were found.

On two occasions the urine of one immunized rabbit was blood free so that the colorimetric method could be employed. After giving 0.08 gm. subcutaneously, 0.002 gm. was excreted during the first four hours. Following a later intravenous injection of 0.01 gm. it was found that one-half the amount given had passed through the kidney within seven hours. Positive results were also obtained in mice injected with urine from these specimens. A normal rabbit which had received 0.01 gm. intravenously was unable to excrete any uranium in seven hours.

From the experiments Gil y Gil concludes that:

1. It is possible to successfully immunize the kidneys of rabbits against poisoning by uranium and sublimate, so that not only frequent toxic subcutaneous, but also intravenous doses, can easily be tolerated.

2. Uranium acts on the glomeruli as well as the tubular system. One apparatus (tubular) may be immunized while the other still continues to show susceptibility.

3. The various segments of the proximal convoluted tubules are not equally immunized. The most marked action is first in the distal segments, which are also most easily immunized, while the medial and proximal divisions are still distinctly sensitive to larger doses.

4. Proof that parenchymatous injury is actual and not concerned with retention of the poison in other places is shown by excretion of the poisonous material in the urine.

5. Immunization is accomplished by partial destruction of the kidney tissue and leads to the characteristic picture of parenchymatous uranium or sublimate contracted kidney.

It is unnecessary here to discuss Gil y Gil's experiments with mercuric chloride immunization since I have repeated his experiments with this poison, the results of which, together with a review of his work are to be published separately.

Criticism of Gil y Gil's Methods and Results.

1. Inadequate control of experiments. The practical importance of knowing as nearly as possible the onset and duration of cell necrosis, the time of appearance of regenerated cells in the location of those killed by the poison, the rate of progress and the time required for complete regeneration cannot be over-emphasized when applied to a study of immunization of specific cells. In the case of renal tubular cells the question of immunity is wholly concerned with the condition of regenerated epithelium, not the original cells, since these always remain susceptible to injury by large amounts of a poison and are therefore an unreliable criterion of immunity. Apparently Gil y Gil did not have a clear conception of which renal tubular cells are immunized. He makes no direct reference to the condition of regenerated tubular cells. Suzuki, the first to recognize the phenomenon of increased resistance of renal cells to uranium states specifically that it is the regenerated epithelium which shows no injury. When it is possible to demonstrate histologically that a cell is undamaged by an equal or greater quantity of the substance capable of killing cells originally in the same location, then and only then can we properly speak of specific cellular immunity.

If one is to be certain what cells were killed by a given injection of poison the examination must be made after unmistakable cellular degenerative changes have had time to develop, while the morphology of the dead cells is still recognizable, and before any or but very slight regeneration takes place. Unless this rule is invariably adhered to, accurate interpretation of findings is most difficult. It becomes next to impossible to determine whether or not the regenerated epithelium is damaged if the animal is allowed to live until regeneration has taken place in the segments affected by the last given dose of poison, since such new cells will appear exactly the same as those which may have been present for weeks or months previously. Gil y Gil himself asserts that the height of necrosis is attained in five or six days and the inference is that after this the action recedes. How then is it possible to allow animals to live until regeneration must be well

advanced, until the destructive process is past its zenith, and then assert, as he does, that immunity is proven by lack of injury to the kidney epithelium? Examining the protocols of his immune series we find that:

Rabbit	J-18	killed	11	days	after	last	injection
"	J-19	"	9	"	"	"	"
"	J-20	"	7	"	"	"	"
"	J-21	"	1	"	"	"	"
"	J-22	"	5	"	"	"	"
"	J-23	"	10	"	"	"	"
"	J-24	"	1	"	"	"	"

It is thus evident that he either considered the length of time after an injection unimportant or in most instances wholly overlooked its importance. Yet if we turn to the records of his non-immunized animals it will be seen that regeneration was found fairly constantly after six days. Whether he believed that no regeneration would take place after administrations of large amounts of uranium and was thus safe in allowing life to continue for as long as eleven days cannot be determined from the text of the article.

No claim of immunity is made for Rabbits J-18, 19, 20 and 22. In J-21 he speaks of glomerular but not tubular immunity. But in this animal hyaline droplet degeneration in the glomerular capillaries is described as abundant, a change which in another place he attributes to the injurious effect of uranium. Such contradictions and ambiguities do not strengthen the proof of immunity.

Rabbits J-23 and 24 were regarded as the best examples of immunization. It will be noted however that J-23 was not studied until *ten days* after the last injection. To say as he does "Bemerkenswert ist, das diese Schrumpfniere trotz der wiederholten schweren Vergiftungen gar keine frischen Nekrosen zeigt, auch keine frischen Affektionen der Glomeruli" proves absolutely nothing because in such a long interval there was ample time for subsidence of injury and for almost complete relining of the damaged tubules by new epithelium, which of course would show no evidence of injury.

2. Subcutaneous and intravenous administrations in the same immune animal.

This should never be done unless the relative ratio in effect between subcutaneous and intravenous doses has been determined. Gil y Gil failed to do this, yet in Rabbit J-24 after subcutaneous administrations up to 80 milligrams, gave intravenous injections, the largest of which was only 10 milligrams, killed the animal a day later, and, finding no fresh lesions, counted this animal the best example of immunization. More convincing proof would be offered had increasingly larger subcutaneous doses been given.

3. Inadequate determination of the lethal dose. At the outset the author states that the factors to be considered in this determination are: (a) use of healthy animals of equal weight, (b) a given time in which death must occur and (c) extrarenal factors. In fairness it must be said he admits that on this basis the lethal dose will be only approximately correct, varying within narrow limits. As to these limits or what the lethal dose was found to be nothing is said. Animals given the same quantity of uranium frequently differed considerably in weight. There is little or no discus-

sion of extrarenal factors. Of the nine rabbits receiving 0.001 gm. subcutaneously more than one-half survived. Two milligrams administered in the same way killed two-thirds of the animals. The smaller number of rabbits given intravenous injections and the wide differences in the amount administered makes impossible any conclusion as to the quantity necessary to cause death when injected in this way.

Author's Experiments.

1. *General Considerations of the Problem of Cellular Immunity.*

In attempting to demonstrate immunity of specific cells for a poison the experimental worker must clearly differentiate between (1) the *fact* or *proof* of immunity and (2) the *mechanism* or *means* by which this phenomenon is made possible.

In (1) the factors involved and procedure to be followed are relatively simple. First, certain criteria of immunity must be established. Of the several possibilities three are at once apparent, namely:

(a) Immunization of the organism as a whole. Here the first step is clearly that of establishing the minimum lethal dose, taking into consideration such factors as individual differances in susceptibility, mode of administration of the poison, weight, age, sex and the presence of complicating disease processes. The number of times the minimal lethal dose which the animal is able to withstand will then indicate the degree of tolerance or immunity attained.

(b) Specific or local cellular immunity. This is of the greatest importance if it can be proven to exist. Fortunately we have in the salts of the heavy metals, particularly of uranium, chromium and mercury, substances which act selectively on certain divisions of the proximal convoluted tubular system producing sharply demarcated and easily recognizable lesions which are ideal for the study of local immunity. That the selective site of injury by uranium is in the distal and transitional parts of the proximal convoluted tubules is readily proven by intravital staining with carmine. Suzuki (21), Möllendorff, (40) and Mitamura (41) have shown that carmine is taken up in varying amounts by the different segments of the proximal convoluted tubules. When the epithelium in any division is destroyed there is no longer a characteristic arrangement of carmine granules in the dead cells thus definitely localizing the lesion. If after allowing sufficient time for cellular regeneration in the affected tubular segments the animal is intravitally stained with carmine it will be noted that the new cells are unstained by the dye, a fact first pointed out by Ribbert (42) and later confirmed by

(40) Möllendorff, W., Vitale Färbungen an tierschen Zellen, Ergebn. d. Physiol. 18: p. 141, 1920.

(41) Mitamura, Tokushiro., Neue Belege zur Ludwig-Cushnyschen Filtrations theorie der Niere (Vorläufige Mitteilung) Pflüger's Arch. f. Physiol. 204: p. 561-571, 1924.

(42) Ribbert, H., Die Abscheidung intravenös injizierten gelösten Karmins in den Geweben, Ztschr. f. allg. Physiol. 4: p. 201-214, 1904.

Oliver (23). The latter procedure although a valuable aid in the recognition of regenerated epithelium is not absolutely essential since the new cells present permanent alterations in histologic and staining qualities which readily distinguish them from original epithelium.

Assuming that the poison is always excreted by the kidney irrespective of the dosage or the pathologic condition of the organ, all that is necessary to prove immunity after establishing the site of injury and the smallest quantity required for constant production of cellular damage, is to allow sufficient time between injections for complete regeneration of cells, increase the dosage and demonstrate that the new cells are uninjured. Using this criterion the degree of cellular immunity may be expressed in multiples of the amount known to kill the original cells in the same location.

(c) Ability of the kidney to excrete a given amount of uranium.

Other factors which must be kept in mind without regard to the criterion used for immunity are:

(a) The possibility of cumulative action. Whether this occurs or not it is essential that the animal be given the opportunity of recovering as fully as possible from the effects of one injection before administering another.

(b) Complications and difficulties in determining the degree of tolerance attained may be avoided by administering the poison wholly subcutaneously or intravenously in any given animal.

(2) Mechanism of the immunity. Many difficult questions are encountered when one attempts to explain the means by which the immunity is accomplished.

Does the substance injure the body as a whole, several organs or systems, or but a single structure? If small quantities are found to affect only the kidney, is the same true for larger doses?

In the case of the kidney numerous questions intimately concerned with the nature and mechanism of renal function arise. The modern view of Cushny, (43) amply confirmed by the recent experimental work of Wearn and Richards (44) is today generally accepted as the best explanation of renal secretion. According to this theory the function of the glomeruli is that of filtration—a purely physical process, while that of the tubules is re-absorption in which the vital activity of the tubular epithelium is assumed to have a part. Uranium must reach the kidney by way of the blood stream and if Cushny's view is accepted the glomeruli are first to come in contact with it. Does part or all of the uranium pass through the glomeruli and exert its effect at the point of selective re-absorption in the proximal convoluted tubules or are the glomeruli also injured? If so what is the effect—immunity with more ready excretion or on the contrary retardation or even inhibition? What is the chemical nature of the injury? Is

(43) Cushny, A. R., The Secretion of the Urine, Longmans, Green and Co., London, 1926.

(44) Wearn, J. T. and Richards, A. N., Observations on the composition of glomerular urine, with particular reference to the problem of reabsorption in the renal tubules. Am. J. Physiol. 71: p. 209, 1924.

the poison held in combination with cell protein? Does regenerated epithelium become tolerant or resistant to the poison rendering re-absorption impossible, or on the other hand are the new cells capable of incorporating and detoxicating it? These questions will be dealt with later in the discussion of results.

2. Material and Methods.

In order to have a basis for comparison of results with those of Gil y Gil the rabbit was selected as the experimental animal.

It appeared necessary first of all to determine the lethal dose of uranium for this animal. Healthy rabbits of both sexes were used, most of which were full grown although a few small and apparently young ones were included. The importance of weight was found to be negligible and in the immunization series no particular attention was paid to it.

A few animals in each subcutaneous and one intravenous series were killed 1 and 3 days after injection to study the evolution of the kidney lesions. Two were intravitally stained with carmine for the purpose of localizing the tubular lesions. Complete necropsies were done in all cases.

In addition to establishing the lethal dose, animals dying from the effect of kidney damage served the useful purpose of following the progress of the lesion over a period of a week or more, thus enabling one to determine when the necrosis reached its zenith and also to study the early stages of epithelial regeneration.

Autopsies were done as soon as possible after death and the tissues placed immediately in both Zenker-formol and formalin. In practically every instance the following stains were employed: hematoxylin-eosin, van Gieson, Mallory's phosphotungstic acid hematoxylin (for hyaline droplet degeneration), potassium ferrocyanide-carmine for iron and Scharlach-R for fat. The kidneys of intravitally stained animals were fixed in formalin, imbedded and cut in the usual manner and counterstained for 20-30 seconds in hemotoxylin.

Rabbits were caged throughout the course of the experiments and kept on a diet consisting of oats, hay, carrots and vegetable trimmings.

In the immunization series the interval between injections was goverened partly by the time found necessary for complete regeneration of epithelium (14 days) and in part by the condition of the animals. It was soon found that the animals reacted much better if a twenty-one rather than a fourteen-day interval was allowed and for the greater part of the time this was adhered to as nearly as practicable.

Chemically pure uranium nitrate (Mallinckrodt) UO_2 (NO_3) 2. 6 H_2O was used. The solutions injected were freshly prepared before each injection, dissolving the crystals in sterile distilled water, at first in the strength of 0.001 gm. of uranium nitrate (including the water of crystallization) to 1 cc. of water. Later as the doses were increased the concentration was raised to 0.002, 0.004 and finally 0.008 gm. per cubic centimeter of solvent. None of these solutions were strong enough to cause local irritation at the site of injection.

3. *The Minimum Lethal Dose.*

(I) Subcutaneous injection.

(a) 0.001 gm. was administered to 33 rabbits varying in weight from 1570 to 3035 gms. Twenty-eight (90.32 per cent) survived, three (9.67 per cent) succumbed within 4-5 days, two were killed for study before three days had elapsed and are not included.

(b) 0.002 gm. Twelve rabbits weighing from 1275 to 2700 gms. received this quantity. Two were killed 1 and 3 days later and are therefore excluded, nine (90 per cent) died between 5 and 13 days after injection. With one exception all deaths occurred between 5 and 7 days. Only one rabbit (10 per cent) survived.

The percentage of animals killed by 0.001 gm. is negligible. On the other hand 0.002 gm. proved fatal in 90 per cent of cases and may therefore be regarded as the subcutaneous minimum lethal dose.

(II) Intravenous injection.

(a) 0.0005 gm. Of the 24 animals given this dose only one failed to survive.

(b) 0.001 gm. was administered to 6 rabbits. Two were killed for study within three days. The four remaining died between 3½ to 4 days after injection. The weights of this group varied from 1000 to 1500 gms.

(c) 0.002 gm. given to two rabbits, each weighing 1400 gms. produced death within three days.

These results show that 0.001 gm. of uranium intravenously constitutes the minimum lethal dose for rabbits.

4. *Acute Uranium Nephritis.*

In order to fully understand the changes observed in the chronic immunized uranium kidney it is necessary first to describe the acute phase of the lesion. Lack of space forbids describing individual cases but it is possible to make a composite description giving the essential changes shown in all acute uranium kidneys. The intensity and extent of the lesions naturally varies with the quantity given, the manner of administration, and the time after injection when the kidney is examined.

It may be stated as a general rule that after a small subcutaneous dose, e. g., 0.001 or 0.002 gm., actual necrosis occurs only in the distal and transitional segments of proximal convoluted tubules, particularly the former, and that the involvement will be rather sharply limited to those tubules situated in the inner part of the cortex. With larger doses however the damage is more extensive, extending into the medial segment of the tubules and spreading into the intermediate and outer cortical zones.

At the end of the first day after administration of a small dose there is very little actual necrosis of epithelium in the segments for which uranium has a specific affinity, although many appear slightly swollen, more granular than normal and their nuclei may exhibit beginning pyknosis or karyolysis. Only a few will be found desquamating into the lumen. The glomerular capillaries are frequently congested, reducing the size of the capsular space. Even at this early stage there is not infrequently a perceptible swelling of

the cytoplasm of the glomerular and Bowman's membrane epithelium.

After three days the cells in the distal and transitional divisions are mostly necrotic. With small doses the necrosis is of the simple type but with larger amounts all dead cells may fuse into hyalin-like homogeneous masses adherent to the basement membrane and almost closing the lumina. The dead cells are seen either partly or wholly detached from the basement membrane and forming loose masses in the lumen. Their cytoplasm is swollen and often thickly set with fine vacuoles which in Scharlach-R preparations prove to be fat. Most nuclei are markedly pyknotic and in varying stages of extrusion from the cell body, others show karyolysis or karyorrhexis and becoming mixed with the dead cellular debris. Not all cells in the affected segments are killed. There always remains here and there a cell or two which though definitely altered in appearance remains alive and attached to the basement membrane. It is from such cells that regeneration largely occurs. Even with large doses the first division of the proximal convoluted tubules remains alive, the cells exhibiting varying degrees of parenchymatous degeneration but rarely necrosis. No perceptible injury is to be detected in the other tubular systems.

The origin of casts and their morphology in the various parts of the tubular system is of interest. The dead epithelium in the affected segments first lies loosely in the lumen but on passing into the descending limb of Henle's loop all form of cell outline is lost, the detritis becoming compact and homogeneous. Although most casts are of this type it is not uncommon to find a few epithelial cells with pyknotic nuclei included in the masses, also nuclear fragments and varying numbers of red blood cells. Most casts contain rounded or oval vacuoles which prove to be fat when stained with Scharlach-R. By the third day the number of casts is enormous, filling nearly all tubules in the cortical medullary rays. Undoubtedly the albuminous material from the glomerular capsular spaces contributes to the formation of casts but certainly the greater part comes from tubular epithelium.

With larger doses glomerular changes become more pronounced, showing either congestion of the capillaries or a filling of the lumina with what appears to be fibrin. The cytoplasm of the cells covering the tufts and Bowman's membrane becomes swollen and granular and not infrequently the cells desquamate into the capsular space forming finely granular masses. Adhesions between the tuft and capsule at one or more points are often seen. Another important lesion occurring in some animals even after very small subcutaneous or intravenous doses is destruction of one or more divisions of the glomerulus with the formation of cyst-like intraglomerular hemorrhages. Less commonly the entire glomerulus is thus destroyed. Whenever such hemorrhages are present some capsular spaces will be found filled with well-preserved red blood cells and in the proximal convoluted tubules pure blood casts may be very numerous. The later stages of these hemorrhagic glomerular lesions are not often observed. In some instances the entire glomerulus disappears and

the space is filled with fibrin and blood, in others where but one or two divisions of the tuft are involved healing takes places by organization of the hemorrhage.

That uranium nitrate injures the glomeruli cannot be doubted. Even when only slight alteration is demonstrable in the covering epithelium careful search will nearly always reveal a few red blood cells in the capsular spaces. This occurs so constantly that it is difficult to believe it could be due to artefact. The cells must escape by diapedesis made possible through injury of the capillary endothelium. Albuminous material in the capsular space also speaks for glomerular damage. The more definite changes such as necrosis and desquamation of epithelium have been mentioned. Sections of the acute uranium kidney fixed in Zenker's fluid and stained with Mallory's phosphotungstic acid hematoxylin show in a considerable proportion of cases the hyaline droplet degeneration, first described by Christian (45) who regarded this change as evidence of glomerular capillary injury. These droplets are rounded bluish-black stained bodies occurring in groups of three to twelve or more within the capillary endothelial cells.

(45) Christian, H. A. A Glomerular lesion of experimental nephritis. Boston M. and S. J. 159: p. 8, 1908.

Increase of wandering cells, chiefly lymphocytes, is usually slight during the acute stage of uranium nephritis. Edema of the interstitial tissue and pelvic fat is quite constantly found.

The height of the destructive process is reached about the fifth day after which time only occasional cells are lost, the injured but viable epithelium regains its normal appearance while casts diminish in number until by the end of 10-14 days very few still remain in the tubules.

Regeneration of Epithelium.

In rabbits I have never observed regeneration earlier than the fourth day after injection but on the fifth day there is always unmistakable evidence of regenerative activity. At this time although most tubules are still filled with granular debris and the membrana propria is for the most part bare, there will be seen varying numbers of large oval nuclei containing a considerable amount of loosely arranged chromatin with one or two nucleoli. Covering these nuclei is a thin layer of bluish staining cytoplasm which may be seen pushing along the barren basement membrane and often blending imperceptibly with that of other new cells. In other places the rapidly proliferating epithelium forms syncytial giant cells which project irregularly into the lumen. Among the obviously newformed cells others having nuclei about the size of normal renal cells and staining very deeply with hematoxylin will be found. There is much evidence to show that these are original tubular cells which, although injured are still viable and the not infrequent pre-mitotic and mitotic figures strongly indicate that from these much of the regenerated epithelium is formed. As time advances the membrana propria is covered over by new cells derived from mitosis of previously existing single cells and extension of the syncytial giant-cell protoplasm with enclosed

nuclei. There is often an over-production of cellular elements so that the regenerated epithelium no longer consists of a single layer but of irregularly densely packed cells in palisades or more frequently in rows two or three deep. By the end of the fourteenth day regeneration is nearly complete. The alteration in size, shape, staining qualities and arrangement of the new epithelium is permanent.

Phagocytosis of necrotic cell material by regenerated epithelium is, in my experience, a fairly common occurrence. Regeneration begins even while the lumina are filled with granular debris and the protoplasmic processes of the new cells push between the granules engulfing and incorporating them within the cytoplasm. The process is readily recognized on account of the striking difference in the staining of the debris and new cell cytoplasm. The possible fate of this debris will be discussed later.

Connective Tissue Proliferation.

The denuded basement membrane remains inactive for several days in the stage of the acute lesion but after five to seven days begins to show signs of activity in the form of increase in size and number of cells which may at times project into the lumen of the tubule. At the same time the intertubular connective tissue cells are rapidly proliferating but in the rabbit rarely grow into the lumina. Dilatation of the tubules proximal to the seat of injury is not the result of occlusion of tubules by necrotic material because this is not present in the early stages but begins only with the proliferation of connective tissue and increases in direct proportion to it.

With repeated injections of increased amounts of uranium there is a repetition of all stages of the acute process. The localization which at first is in the inner cortex is now found in patches scattered irregularly throughout the intermediate and outer cortical zones. With increased dosage the medial segments of proximal convoluted tubules are killed but this is rarely the case with the first divisions. As the tubular epithelium is gradually destroyed and replaced by new cells the accompanying connective tissue increase likewise becomes more extensive, producing marked distortion of histological pattern. Contraction of the scar tissue of the subcortical zone gives rise to the finely granular surface of a typical secondary contracted kidney. On cut section the chronic uranium kidney constantly presents a definite line of scar tissue at the cortico-medullary boundary and extending irregularly outward toward the capsule.

5. *Immunization Experiments.*

After having determined that 0.001 gm. subcutaneously and half this quantity intravenously constantly kills original renal tubular cells, but not the animal, the next step was to begin with these doses and by gradually increasing the amount attain the highest degree of tolerance possible.

Table 1 shows the general plan followed in each series, the total number of animals and those in each group showing immunization. Animals living long enough after the last injection for regenerative changes to take place have without exception been excluded. Likewise a number of rabbits which survived only the first few doses, even

though some had well developed chronic nephritis and exhibited no evidence of injury to regenerated epithelium have been omitted because the degree of immunity was not great enough to be of much value.

Tables II and III give the essential data in all successfully immunized rabbits. With the exception of the two groups in which an attempt was made to repeat Gil y Gil's experiments a definite plan of increasing the dosage was followed. In the series in which the doses were increased by doubling each previous amount, it was apparent that this could not be carried too far and for this reason the later doses correspond to one-fourth or one-half of the computed amount of double the last dose.

The large number of animals makes it impossible to describe each in detail but since all are essentially alike, differing only in unimportant details, the description of a few will suffice.

Rabbit 4-A.

Gross Examination.—Weight 2770 gms. Slight edema of subcutaneous tissue at site of last injection. Body nourishment good. No ascites or hydrothorax. Urinary bladder contains 2 c. c. of cloudy urine. On section the liver is soft, friable, and distinctly fatty.

TABLE I.—General plan of increasing dosages in the various immunization groups.

Series	Method of Administration	Method of increasing doses	Number rabbits in series	Number regarded as immune	Number not included in immune series
A	Subcutan.	doubling each previous dose	13	5	7
	Subcutan.	tripling each previous dose	6	0	6
GyG	Subcutan.	as in GyG Rabbit J.23	6	0	6
	Subcutan. and Intraven.	as in GyG Rabbit J.24	11	2	9
B	Intraven.	doubling each previous dose	18	6	12
	Intraven.	tripling each previous dose	6	4	2
			60	17	42

TABLE 11.—Essential data of animals in Immunization series A and GyG.

Rabbit and Series	Weight gms.	Dates of Injection	Amount of Uranium gm.	How Given	Fate	Lived After Last Inj Days	Total Time From First Injection Days
	2400	5-18-26	0.001	Subcut			
	2000	6- 1-26	0.002	"			
	2250	6-15-26	0.004	"			
	2050	7- 6-26	0.008	"			
4-A	2120	7-27-26	0.016	"	D	2	226
	2300	8-17-26	0.032	"			
	2360	9- 7-26	0.064	"			
	3050	12- 7-26	0.080	"			
	2840	12-28-26	0.096	"			
	2500	5- 4-26	0.001	"			
	2750	5-18-26	0.002	"			
	2350	6- 1-26	0.004	"			
	2550	6-15-26	0.008	"			
5-A	2400	7- 6-26	0.016	"	D	2	128
	2420	7-27-26	0.032	"			
	2525	8-17-26	0.064	"			
	2665	9- 7-26	0.096	"			
	2500	5-18-26	0.001	"			
	2000	6- 1-26	0.002	"			
	2150	6-15-26	0.004	"			
	1690	7- 6-26	0.008	"			
9-A	1830	7-27-26	0.016	"	D	2	157
	2225	8-17-26	0.032	"			
	2380	9- 4-26	0.064	"			
	2300	9-28-26	0.080	"			
	2290	10-19-26	0.096	"			
	2300	5-18-26	0.001	"			
	2000	6- 1-26	0.002	"			
	2075	6-15-26	0.004	"			
11-A	2070	7- 6-26	0.008	"	D	2	114
	2325	7-27-26	0.016	"			
	2370	8-17-26	0.032	"			
	2470	9- 7-26	0.064	"			
	2300	5-18-26	0.001	"			
	1900	6- 1-26	0.002	"			
	2175	6-15-26	0.004	"			
12-A	2100	7- 6-26	0.008	"	D	3	115
	2400	7-27-26	0.016	"			
	2385	8-17-26	0.032	"			
	2365	9- 7-26	0.064	"			

TABLE II—CONTINUED

Rabbit and Series	Weight gms.	Dates of Injection	Amount of Uranium gm.	How Given	Fate	Lived After Last Inj Days	Total Time From First Injection Days
	2500	6-16-26	0.001	"			
14-GyG	1970	7- 6-26	0.008	"			
J.24	2265	7-27-26	0.030	"	D	8-20	62
	2290	8-17-26	0.080	"		hr	
	2400	6-16-26	0.001	"			
	2170	7- 6-26	0.008	"			
	2285	7-27-26	0.030	"			
15-GyG	2400	8-17-26	0.080	"			
J.24	2365	9- 7-26	0.002	Intraven	K	2	127
	2530	9-28 26	0.005	"			
	2515	10-19-26	0.010	"			

TABLE III.—Essential data of rabbits in Immunization series B.

Rabbit and Series	Weight gms.	Dates of Injection	Amount of Uranium gm.	How Given	Fate	Lived After Last Inj Days	Total Time From First Injection Days
	2400	5-22-26	0.0005	Intraven			
	2000	6- 1-26	0.001	"			
	2250	6-16-26	0.002	"			
	2075	7- 3-26	0.004	"			
BAI-B	2420	7-24-26	0.008	"	D	2	149
	2560	8-14-26	0.016	"			
	2730	9- 4-26	0.024	"			
	2850	9-25-26	0.032	"			
	2690	10-16-26	0.040	"			
	1600	6- 5-26	0.0005	"			
	1600	6-19-26	0.0005	"			
	1450	7- 3-26	0.001	"			
	1600	7-24-26	0.002	"			
BCI-B	1820	8-14-26	0.004	"	K	3	190
	2005	9- 4-26	0.008	"			
	2210	9-25-26	0.015	"			
	2310	11-27-26	0.024	"			
	2250	12-18-26	0.032	"			

TABLE III—CONTINUED

Rabbit and Series	Weight gms.	Dates of Injection	Amount of Uranium gm.	How Given	Fate	Lived After Last Inj Days	Total Time From First Injection Days
	1500	6- 5-26	0.0005	"			
	1600	6-19-26	0.0005	"			
	1550	7- 3-26	0.001	"			
	1785	7-24-26	0.002	"			
	2020	8-14-26	0.004	"			
BGI-B	2135	9- 4-26	0.008	"	K	1½	227½
	2240	9-25-26	0.016	"			
	2475	11-27-26	0.024	"			
	2250	12-18-26	0.032	"			
	1770	1- 3-27	0.040	"			
	1850	1-17-27	0.048	"			
	1650	6-19-26	0.0005	"			
	1500	7- 3-26	0.001	"			
	1680	7-24-26	0.002	"			
BJI-B	1850	8-14-26	0.004	"	K	3	122
	1725	9- 4-26	0.008	"			
	1720	9-25-26	0.016	"			
	1370	10-16-26	0.024	"			
	1500	6-19-26	0.0005	"			
	1550	7- 3-26	0.001	"			
	1810	7-24-26	0.002	"			
	2065	8-14-26	0.004	"	D	1	162
BLI-B	2210	9- 4-26	0.008	"			
	2400	9-25-26	0.016	"			
	2390	10-16-26	0.024	"			
	2560	11- 6-26	0.032	"			
	2560	11-27-26	0.040	"			
	1350	7- 3-26	0.0005	"			
	1640	7-17-26	0.001	"			
	1985	8-14-26	0.002	"			
	2100	9- 4-26	0.004	"			
BQI-B	2450	9-25-2	0.008	"	D	1	148
	2430	10-16-26	0.016	"			
	2710	11- 6-26	0.024	"			
	2630	11-27-26	0.032	"			
	1240	7-17-26	0.0005	"			
	1160	7-31-26	0.0005	"			
	1270	8-21-26	0.001	"			
BSI-B	1430	9-11-26	0.003	"	D	3	101
	1490	10- 2-26	0.009	"			
	1450	10-23-26	0.027	"			

TABLE III—CONTINUED

Rabbit and Series	Weight gms.	Dates of Injection	Amount of Uranium gm.	How Given	Fate	Lived After Last Inj Days	Total Time From First Injection Days
	1510	7-31-26	0.0005	"			
	1450	8-21-26	0.0005	"			
	1680	9-11-26	0.001	"			
BTI-B	1530	10- 2-26	0.003	"	K	2	108
	1450	10-23-26	0.009	"			
	1400	11-13-26	0.027	"			
	1730	7-31-26	0.0005	"			
	2000	8-21-26	0.0005	"			
	2380	9-11-26	0.001	"			
BWI-B	2380	10- 2-26	0.003	"	K	3	130
	2500	10-23-26	0.009	"			
	2490	11-13-26	0.027	"			
	2220	12- 4-26	0.036	"			
	1580	7-31-26	0.0005	"			
	1320	8-21-26	0.0005	"			
	1590	9-11-26	0.001	"			
BXI-B	1620	10- 2-26	0.003	"	K	3	109
	1720	10-23-26	0.009	"			
	1720	11-13-26	0.027	"			

Kidneys.—Combined weight 17.5 gms. Capsules definitely adherent to parenchyma and strip with slight but obviously increased difficulty exposing surfaces which are finely and diffusely granular, brownish in color with many light yellowish-brown pin-point-sized areas raised above the surrounding parenchyma. The organs cut with some difficulty, the cut surfaces show total obliteration of the normal markings in the cortex with here and there fine white scars, particularly marked at the cortico-medullary boundary.

Microscopic.—Everywhere in the cortex there is marked diminution of proximal convoluted tubules retaining the original epithelium and in these marked alteration is noted, consisting of all gradations from parenchymatous and fatty degenerative infiltration to complete necrosis and desquamation. The nuclei are for the most part pyknotic but some show karyorrhexis or karyolysis. Some cells are still viable. There is no evidence of beginning regeneration in these locations.

Many proximal convoluted tubules are lined by typical appearing regenerated epithelium, irregular, often flattened and with dark bluish-pink staining cytoplasm and oval hyperchromatic nuclei. In the cytoplasm of some of these cells there is yellowish-brown granular pigment. Pigment is also found in the lumina of regenerated tubules, particularly those with very small lumina. That some regenerated

tubules are patent and connected with the damaged proximal segments is shown by the presence of desquamated epithelium recognizable as original cells. Hyaline droplet degeneration occurs in some original tubular cells but not in the regenerated epithelium. Very rarely is there any demonstrable strands resembling amorphous phosphates of the urine are seen.

Glomeruli.—There is wide variation in size, some being four or five times larger than others. The hypertrophied glomeruli are well filled with blood. A moderate degree of cystic dilatation of the capsular spaces is frequently

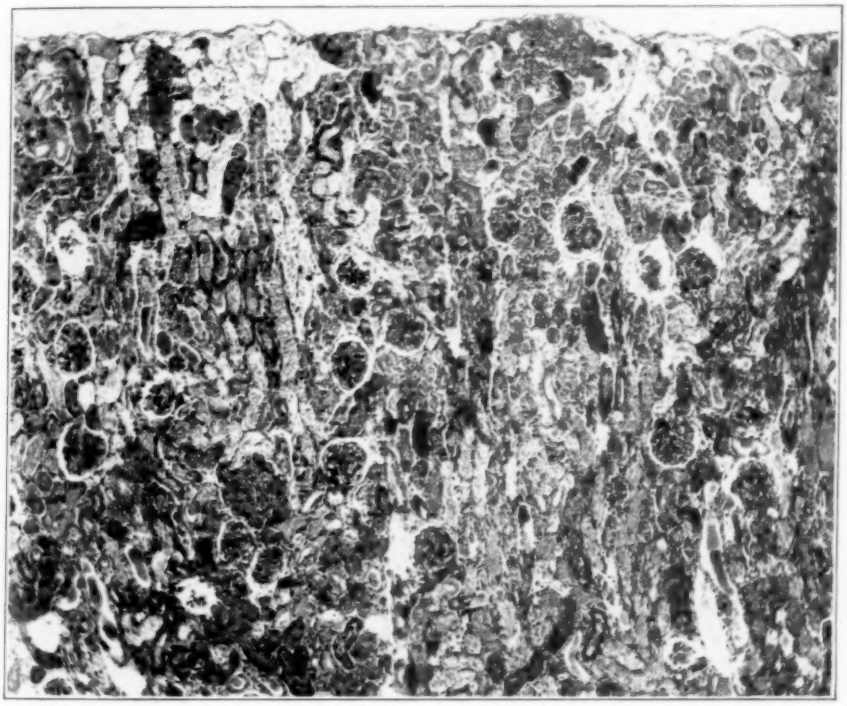

FIG. 1.—Low power photomicrograph of entire kidney cortex showing extent and distribution of lesions on the sixth day after subcutaneous injection of 0.009 gm. uranium nitrate. Necrosis of epithelium in distal and transitional divisions of proximal convoluted tubules in all zones of cortex. Many casts still present.

histological evidence of injury in the regenerated cells. The epithelium of other tubular systems is uninjured. A striking feature is the marked dilatation of the tubules in the cortical rays. Casts are not numerous. Those present are predominantly of the mixed hyaline-fatty-epithelial variety, while in many collecting tubules ropy beaded

observed and in these dilated spaces there is usually some finely granular or homogeneous pinkish staining material. No intraglomerular hemorrhages are present nor are red blood cells found in the glomerular spaces. Increase in number of cells of Bowman's membrane is the rule, varying in degree from slight to very pronounced

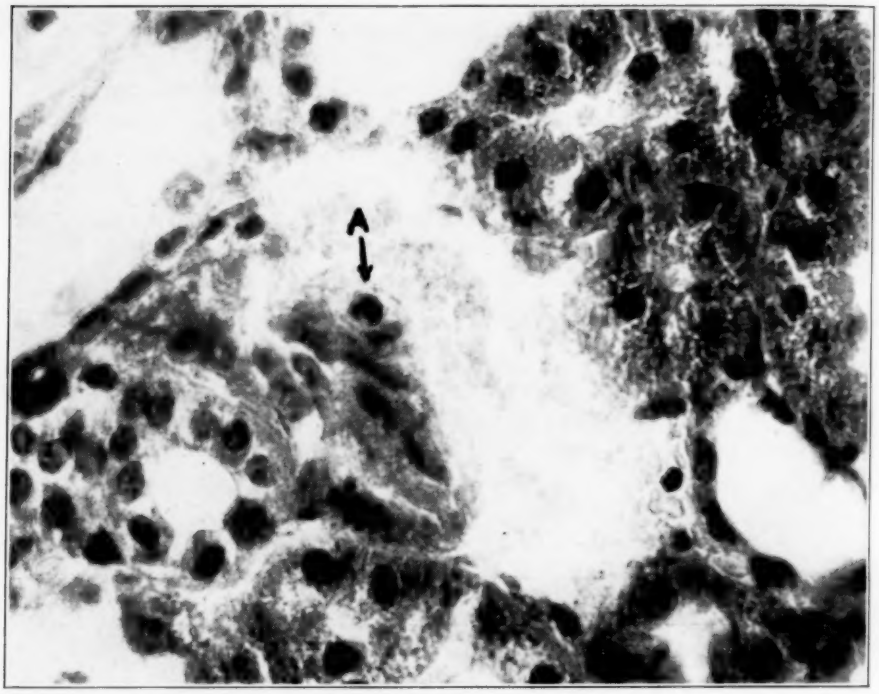

FIG. 2.—Oil immersion. Rabbit 3-A. Last injection of uranium four days before death. At 'A' is an original proximal convoluted tubular cell, which, although injured, is still viable. It is from such cells that regeneration of epithelium largely takes place.

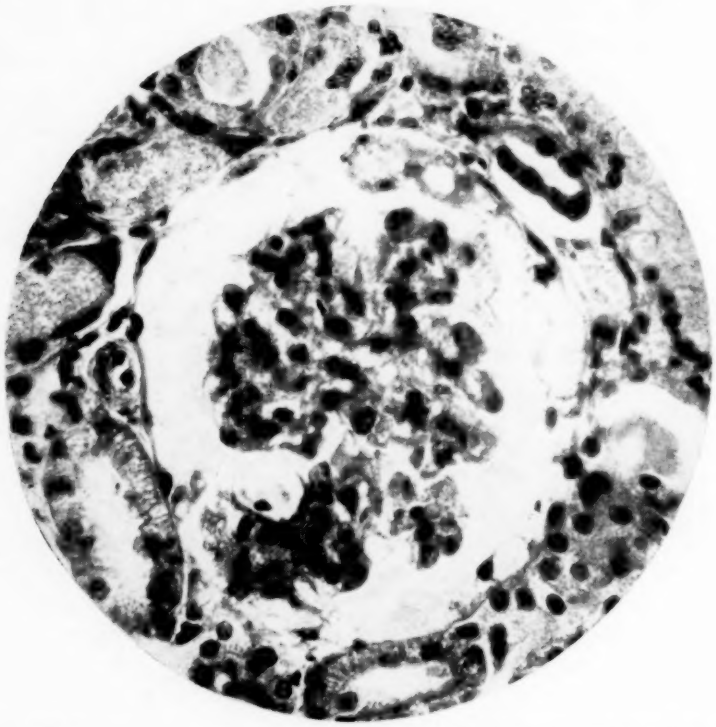

FIG. 3.—Oil immersion. Glomerular damage after 0.009 gm. of uranium subcutaneously. Bowman's membrane epithelium is markedly edematous and some of the cells are undergoing necrosis. The same is true of the covering epithelium of the tuft.

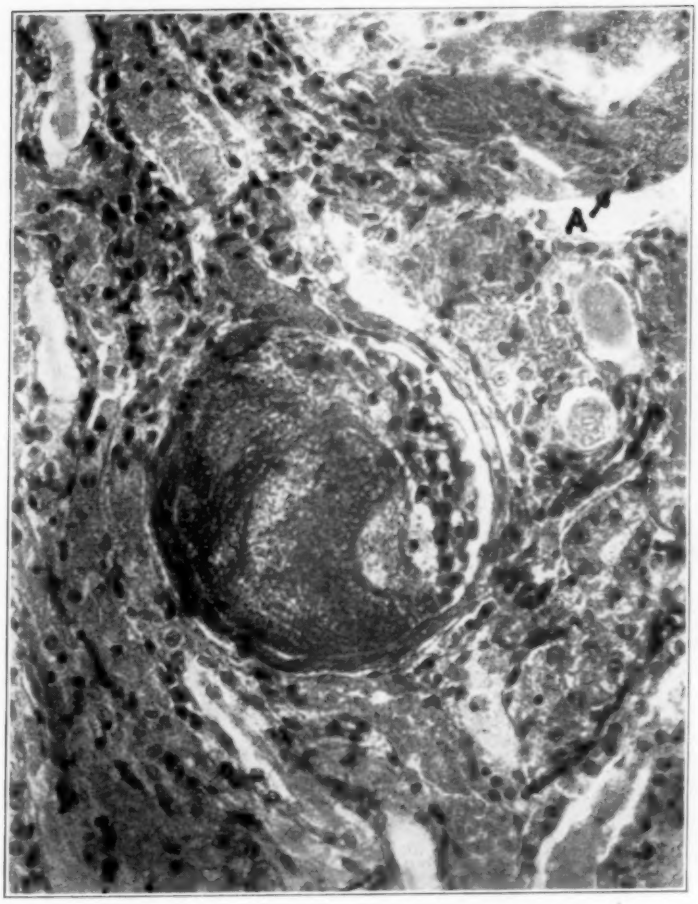

FIG. 4.—Rabbit 23-GyG-J-23. High power. Two milligrams uranium nitrate subcutaneously; death on fifth day. Recent large intraglomerular hemorrhage with destruction of most of the tuft. Strands of fibrin are seen within the clot. At 'A' is a convoluted tubule plugged with red blood cells.

and often forming epithelial crescents which contain vacuoles. Adhesions between the crescents and the glomerular tufts often occurs while glomeruli in which the capsular space is entirely obliterated by a concentric overgrowth of Bowman's membrane epithelium are not rare. Such glomeruli are atrophic and have collapsed and empty vessels. Hyaline droplet degeneration is found in only two of one hundred glomeruli examined.

Van Gieson's preparations show very pronounced interstitial scarring everywhere in the cortex and at the border zone between cortex and medulla, fully as marked in the labyrinths as in the rays. A few small collections of lymphocytes may be seen in the interstitial tissue. The changes occurring in and about the glomerular capsules are best studied with this stain. It is seen that the proliferating epithelium of Bowman's membrane

undergoes hyaline degeneration, the membrana propria is always thickened and stains red rather than yellow. A common finding is a concentric ring of fibrous tissue, often quite thick, just outside the membrana propria. The adventitia of arcuate and interlobular arteries shows definite increase but no change is observable in the media or intima.

Fat droplets are found in small numbers in the epithelium of the ascending limbs of Henle, small collecting tubules of the cortex, necrotic epithelium and casts but none are present in the regenerated epithelium.

The pigment contained in regenerated epithelium is negative for iron, retaining the yellowish-brown color seen with other stains.

Liver.—Sections show well marked fatty degenerative infiltration involving the entire lobules but most marked toward the central veins. The findings are confirmed by specific fat stains. The nuclei of cells containing the greatest amount of fat are pyknotic. No mitoses or other evidences of regeneration are found in the liver.

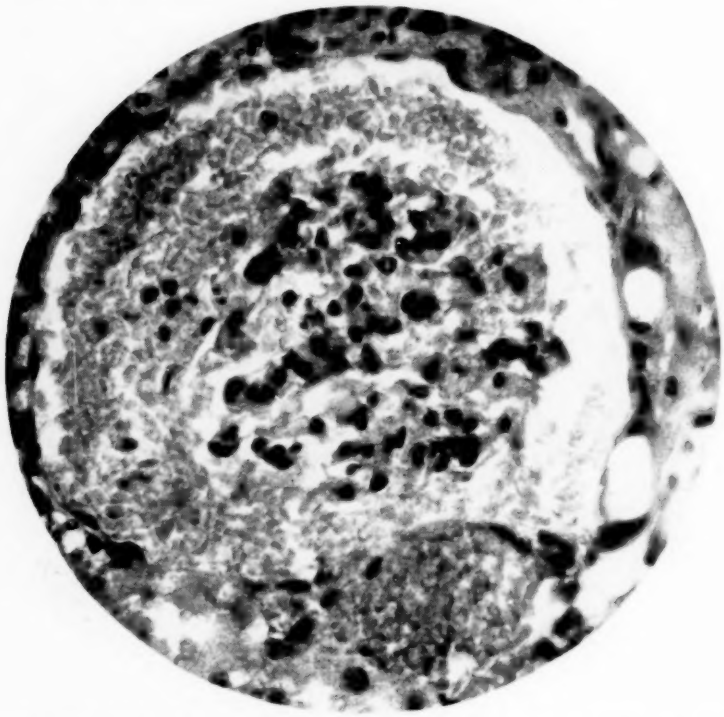

FIG. 5.—Rabbit 83-A. Oil immersion. Died five days after injection of 0.081 gm. of uranium. Extensive fresh hemorrhage into the capsular space. An adjacent tubule is also filled with blood.

Rabbit 15-*GyG-J.24.*

Necropsy.—Animal killed. Weight 2400 grams. No noteworthy pathology except in kidneys.

Kidneys.—Combined weight 19 gms. The capsules are slightly adherent and

when stripped off expose finely granular light brownish surfaces. Definite resistance to the knife on sectioning. The cortical markings are absent and there are fine whitish scars, most marked at the junction of cortex and medulla.

variation in the size of various tubules and the presence of some casts.

In this case the convoluted tubules with original epithelium appear more localized in the intermediate cortical zone than usual, with but very few in the inner and outer zones. The only

FIG. 6.—Camera lucida drawing from kidney of acute uranium nephritis showing within the glomerular capillary endothelium the 'hyaline droplet degeneration' first described by Christian. Mallory's phosphotungstic acid hemotoxylin stain.

Microscopic.—The usual picture of extreme chronic nephritis is present, characterized by much scarring with obliteration or distortion of the normal markings in the cortex, great diminution of proximal convoluted tubules with original epithelium, considerable regeneration in these tubules, marked epithelial damage found is in this original proximal convoluted tubular epithelium. No regenerative activity is noted in these locations. The regenerated epithelium is everywhere intact. Casts are numerous in the regenerated tubules, some loosely granular, others densely hyalin, others contain-

FIG. 7.—Rabbit 20-GyG-J-23. Oil immersion. 'A' is a segment of proximal convoluted tubule almost fully relined by new epithelium within five days after the administration of 0.002 gm. of uranium. The new cells are flattened and have oval hyperchromatic nuclei; a mitotic figure is seen along the right border. At this point the section is cut through the tubule wall giving the impression that some of the cells are within the lumen. 'B' indicates a proximal convoluted tubule retaining the original epithelium. 'C' is also a division of a proximal convoluted tubule in which the epithelium has been destroyed by the uranium and in which there is as yet no regenerative activity.

ing well preserved red blood cells or blood pigment. Mallory's stain reveals moderate numbers of coarse round droplets in many original proximal convoluted tubular cells. Fat is likewise present in these cells, in the smaller collecting tubular epithelium and abundantly in some casts but only rarely in the regenerated cells.

Glomeruli.—Cystic dilatation of the capsular spaces is striking, particularly toward the inner cortex where the scarring is most marked and where there is little regeneration of tubular epithelium. The dilatation is often extreme and in these instances the glomeruli are atrophic and sometimes flattened out along the capsule. In nearly

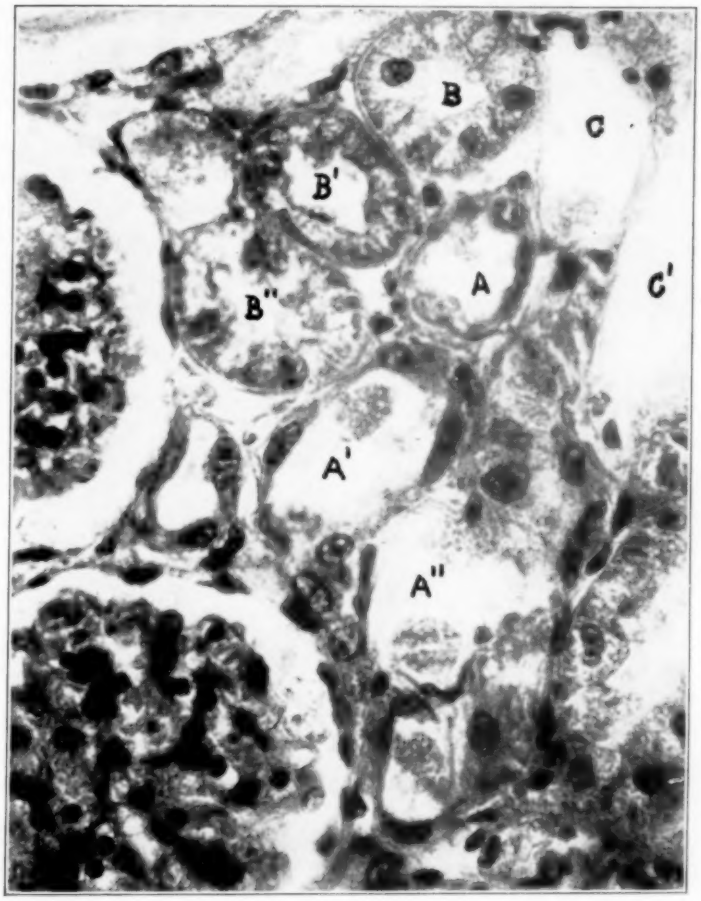

FIG. 8.—High power photomicrograph from same kidney shown in Fig. 7. Several cross-sections of proximal convoluted tubules (A, A^1, A^{11}) are partially covered by new epithelium. B, B^1, B^{11} are uninjured segments of the same tubule. At C and C^1 regeneration has not started. The striking difference in histologic characteristics of the new and old epithelium is very apparent. In the tubular lumina and glomerular capsular spaces are a few necrotic epithelial cells.

all the marked cystic spaces there is pinkish staining material, rarely a few red blood cells or desquamated epithelial cells. Proliferation of Bowman's epithelium is slight except in rare instances where two or three layers of cells form an epithelial crescent. No instances of complete obliteration are found. Hyaline droplet degeneration of the glomerular capillaries is lacking.

Van Gieson's stain discloses extensive interstitial connective tissue increase in all parts of the cortex. The adventitia of most arcuate and interlobular arteries is increased and directly continuous with the intertubular scarring. The usual iron-free pigment occurs in regenerated epithelial cells.

Liver.—Necrosis of an occasional hepatic cell near central veins. No

fatty degenerative infiltration. Slight chronic pericholangitis.

Rabbit BGI-B.

Autopsy Findings.—Poorly nourished, weight 1800 gms. No subcutaneous edema, hydroperitoneum or hydrothorax. Two cubic centimeters of urine in bladder. Several small consolidations in left lung, also purulent bronchitis. Liver is distinctly fatty.

Kidneys.—Combined weight 10 gms. visibly decreased in size. Capsules slightly adherent to parenchyma. Cortical surface finely granular throughout. Definitely increased resistance encountered on sectioning. Cut surfaces show cortex thinner than normal and thickly set with fine whitish scars, normal markings entirely lacking.

Microscopic.—The very extreme chronic nephritis in this animal compares favorably with that in the subcutaneous series receiving the largest injections and living the same length of time. Scarring and distortion in the cortex is so extreme that it is practically impossible to recognize the labyrinths and rays. Proximal convoluted tubules with original epithelium are very rare but when found exhibit slight evidence of injury. Many regenerated tubules may be seen in the cortex and the epithelium of these is quite intact. Casts are not numerous. Granular pigment occurs in the cytoplasm of new epithelial cells and in the lumina of regenerated tubules. Preparations stained for fat show this substance in the persisting original convoluted tubular cells, the ascending limbs of Henle and very abundantly in the casts.

Glomeruli.—Because of the extensive scarring and subsequent contraction the glomeruli are numerous in every microscopic field. Many are markedly atrophic but others are hypertrophic and congested. Complete obliteration of the capsular space by an overgrowth of Bowman's epithelium is fairly common as is also cystic dilatation of this space. Hemorrhages are not found either in the glomerular tufts of capsular spaces nor is hyaline droplet degeneration present in the capillary walls.

In the van Gieson's preparations there is seen a very extensive interstitial connective tissue increase everywhere in the cortex. In the scar tissue are moderate numbers of lymphocytes, both diffuse and in collections.

The pigment in regenerated cells and tubules contains no iron.

Liver.—Well marked fatty degenerative infiltration throughout the lobules.

Lung.—Unresolved organizing lobular pneumonia, purulent bronchitis.

Rabbit BXI-B.

Two cubic centimeters of 5 per cent lithium carmine injected intravenously 48, 24, and 3 hours before last administration of uranium. An additional cubic centimeter of carmine was given 24 hours after the dose of uranium. Killed 3 days after giving uranium.

Autopsy.—Weight 1670 gms. Skin, conjunctivae, mucous membranes, and skeletal musculature stained pinkish with carmine. No edema or free fluid in peritoneal or pleural cavities. Bladder contains 6 c. c. of carmine red urine. Left epididymis contains numerous small abscesses. Gall bladder is filled with glairy mucus.

Kidneys.—Combined weight 18 grams. Capsules not adherent, sur-

faces only slightly irregular and deep reddish brown. On section the parenchyma appears deep reddish and the normal markings are quite distinct on account of the alternate deep carmine red and pale streaks. Fine scarring is visible at the border of the cortex and medulla.

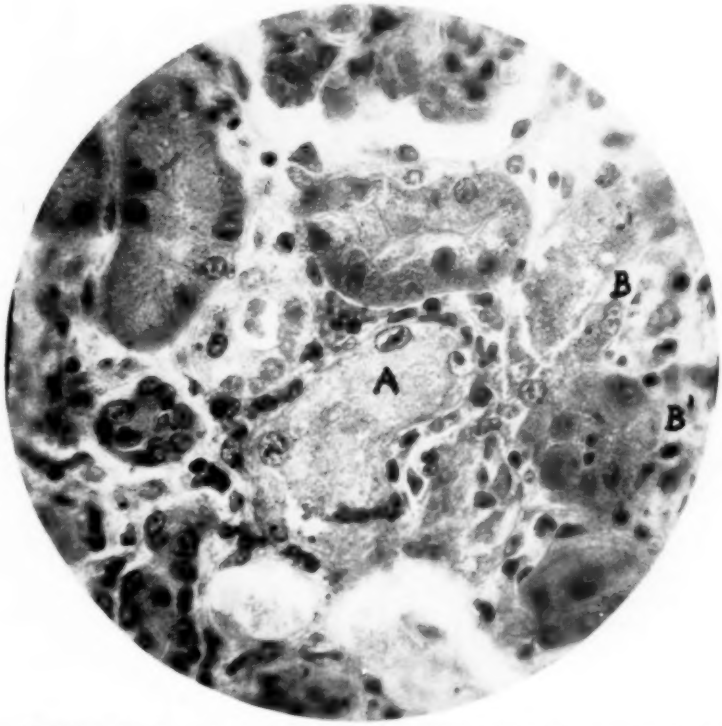

FIG. 9.—Rabbit BXI-B. Oil immersion. 'A' is a tubule lined by regenerated epithelium in the lumen of which there is carmine-stained detritus, indicating that the tubule is patent. At B and B^1 are two segments in which the original epithelium is undergoing necrosis. The final dose of uranium given three days previously was fifty-four times that known to kill original epithelium, yet there is no evidence of damage to the new cells.

Microscopic. — Intravital preparations show in all zones of the cortex one to three cross sections of proximal convoluted tubules with original epithelium located about the glomeruli, readily recognized because they are the only tubules which have taken up the carmine. Closer study reveals the heavy impregnation which occurs only in the first segment. Most of these cells are uninjured although an occasional one is found in which the nucleus stains red, a sign of cell death. Just beneath the capsule are numerous tubules filled with faintly carmine stained cellular debris. The carmine staining and close proximity to the first segments indicates that these are second divisions of proximal convoluted tubules damaged by the last dose of uranium. No original epithelium of the third and fourth segments remains. Tubules with typical-appearing uninjured regenerated epithelium are found in the regions

FIG. 10.—Rabbit 4-A. Oil immersion. A and A^1 are parts of a proximal convoluted tubule in which there is necrosis of the original cells, while in B, B^1 and B^{11} the regenerated cell linings exhibit no evidence of injury. The patency of the latter tubules is evidenced by the presence of cellular detritus and well preserved red blood cells within their lumina. The last amount of uranium administered two days before was ninety-six times the initial dose.

just described and these cells fail to stain with carmine. That many of these tubules are patent is shown by the presence within their lumina of carmine colored dead cells or cellular detritus. Casts stained with carmine are also numerous in the limbs of Henle's loop and the smaller collecting tubules, further proving the patency of the regenerated tubules since in no other way could the carmine reach the collecting tubules. Carmine is not found in any tubular epithelium except as above described. In some connective tissue cells and leukocytes there is a considerable amount of the stain. A few carmine emboli occur in the glomerular vessels but most of the stain here is within polymorphonuclear leukocytes.

In hematoxylin and eosin preparations there is no evidence of necrosis

in any of the new epithelium. Granular yellowish-brown pigment is abundant in the cytoplasm of many of these cells but is negative for iron.

The glomeruli present the usual picture of chronic uranium nephritis although atrophy is not extreme and cystic dilatation is not marked. Hyaline droplet degeneration of the capillary walls is absent. There is the usual

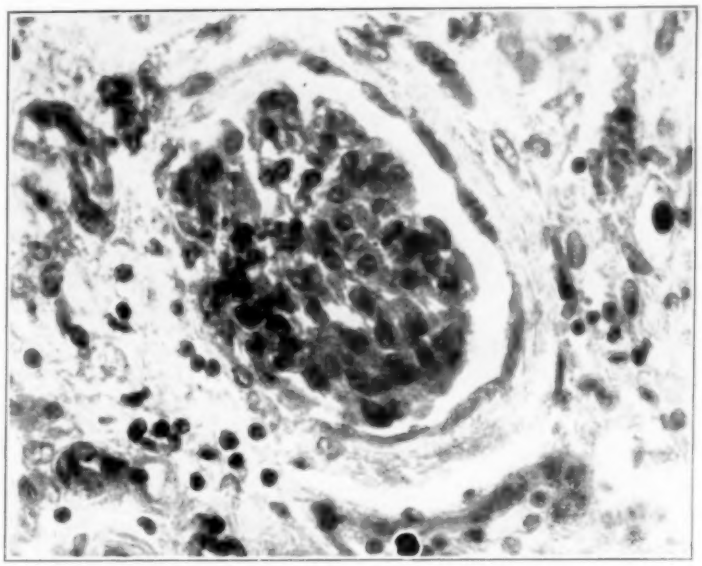

Fig. 11.—Rabbit 4-A. Oil immersion. Thickening and hyalin degeneration of membrana propria about glomerulus. Slight increase in number of cells of Bowman's membrane. Atrophy of glomerulus.

proliferation of Bowman's epithelium with the formation of an occasional crescent or obliteration of the capsular space.

Sections stained with van Gieson's mixture show the same changes described in other cases.

Liver.—Carmine is deposited in the reticulo-endothelial and stellate cells. No fat.

Gall Bladder.—Chronic catarrhal cholecystitis.

Epididymis. — Subacute purulent epididymitis.

Discussion of Results.

The pathologic-histological alterations in the kidneys described are typical of all included in the immune series, varying only in degree. With regard to the condition of the regenerated epithelium and functioning glomeruli there is absolute agreement in all; in none is there any appreciable damage to these structures while in every one there is demonstrable injury to the original proximal convoluted tubular cells.

Experiments on non-immunized rabbits show that 0.001 gm. of uranium subcutaneously and 0.005 gm. intravenously is sufficient to produce cell death in the distal and transitional divisions of proximal convoluted tub-

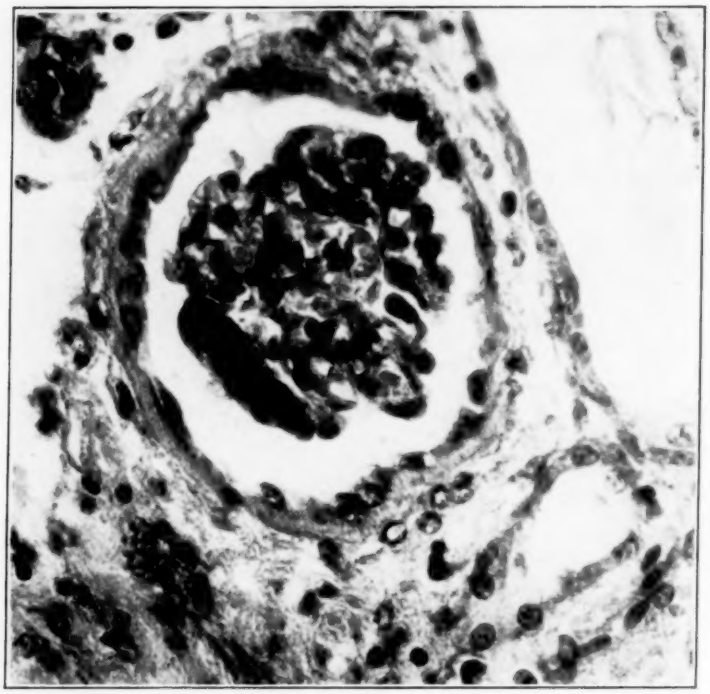

FIG. 12.—Rabbit 4-A. Oil immersion. Well marked hyperplasia of epithelium of Bowman's membrane. The glomerular capillaries contain a fair amount of blood.

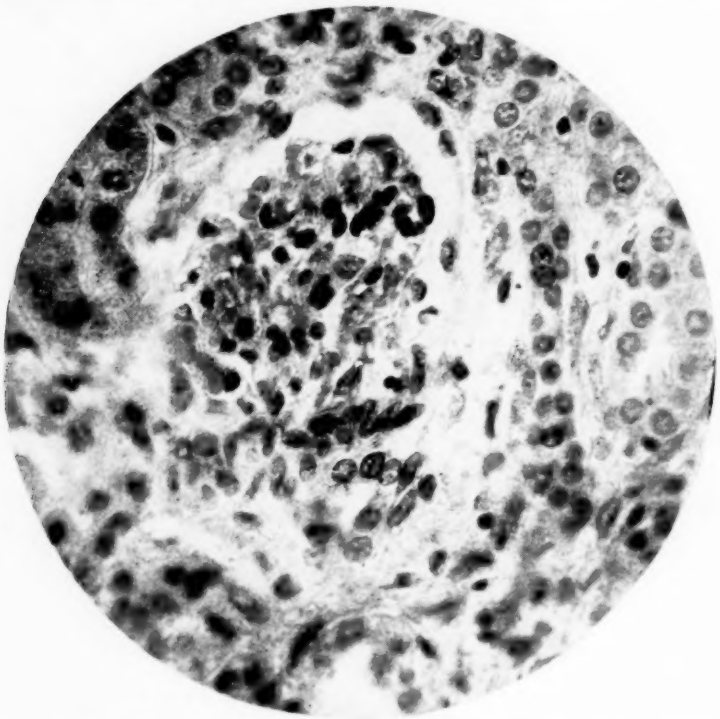

FIG. 13.—Rabbit BQI-B. Oil immersion photomicrograph showing a large epithelial crescent. Some capillaries in the tuft are well filled with blood.

ules and definite evidences of injury in the glomeruli. In immune series A, 64 to 96 times, and in Series B, 54 to 96 times, these amounts were administered without damaging the regenerated cells or the glomeruli.

found in the glomerular capillaries, the persisting epithelium of proximal convoluted tubules, dead epithelium in the lumina of some regenerated tubules, limbs of Henle and collecting tubules. Regenerated epithelium does

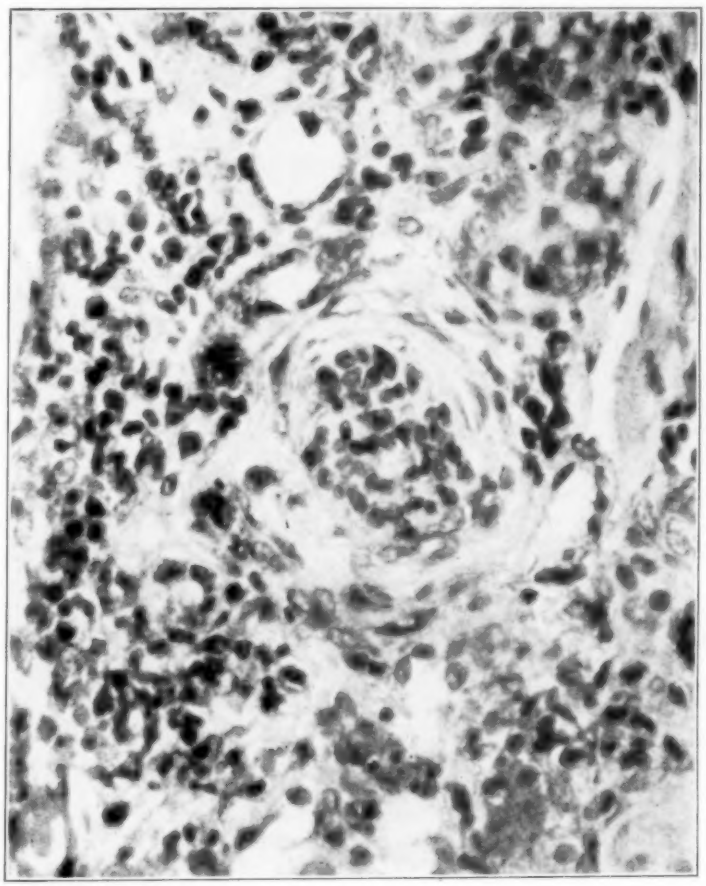

FIG. 14.—Rabbit BGI-B. High power. Obliteration of capsular space resulting from overgrowth of Bowman's epithelium. Marked glomerular atrophy. Numerous lymphocytes in the interstitial tissue.

That many glomeruli and regenerated tubules are patent in the chronic uranium kidney is demonstrated by the microscopic findings in three animals intravitally stained with carmine (BLI, BTI, BXI). In all the stain was not stain with carmine and for this reason any cells stained with the dye and found in the tubules must originate from some point nearer the glomerulus. Furthermore the carmine in Henle's loops and collecting tubules

could reach these only after having passed through the proximal convoluted tubular units. It is not unreasonable to suppose that if carmine is able to reach the various structures mentioned uranium might do likewise. Necrosis of the original convoluted tubular cells is of the type produced by slowly. From the tables it will be seen that after the first two or three injections the rabbits frequently gained in weight and often weighed several hundred grams more at the end of the experiment than at the beginning. After the first few injections it was uncommon for the animals to refuse food for

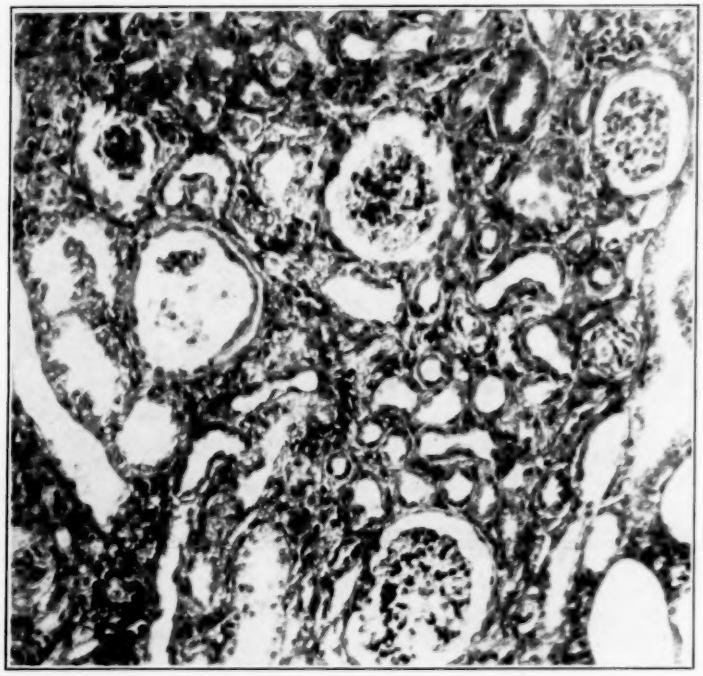

FIG. 15.—Rabbit BGI-B. Low power photomicrograph showing a portion of a labyrinth well illustrating the pathologic changes constantly seen in the chronic uranium kidney. Very few proximal convoluted tubules with original epithelium remain; most of the tubules are lined by new epithelial cells. Some glomeruli are atrophic, others are hypertrophic. Pronounced increase in interstitial tissue.

uranium and there is no reason to believe that some of the poison did not come in contact with the regenerated tubules containing carmine stained detritus, yet in these there is no evidence of injury.

The highest percentage of immunization was obtained in Series A and B in which the dosage was increased more than the first day or two and many exhibited no symptoms whatever.

The attempt to carry out Gil y Gil's procedure in his rabbit J.23 met with complete failure. Only one rabbit survived the initial dose of 0.002 gm. and this one died when the next dose of 0.008 gm. was given. But little better success was obtained with the tech-

nique employed in his J.24. Six rabbits succumbed after the second injection (0.008 gm.) and three more following the increase from 0.03 to 0.08 gm. and of these two were over the fore any appreciable degree of immunity is attained.

Increasing the dosage by multiples of three proved unsatisfactory in the subcutaneous series because all ani-

FIG. 16.—Low power photomicrograph of entire kidney cortex of a mouse injected subcutaneously with 2 c. c. of urine from Rabbit 4-A on the second day after the rabbit had been given 0.064 gm. of uranium. The proximal convoluted tubules nearest the medulla show extensive necrosis of epithelium which has desquamated into the lumina. The type of the lesion and its location is identical with that of acute uranium nephritis in rabbits.

4-5 day limit and could not be included in the immune series because of regeneration having begun. Only one rabbit survived the entire series of doses. Such a rapid increase in dosage is unwise because most animals die be-

mals died after the increase from 0.027 to 0.081 gms. and unfortunately after the beginning formation of new cells which necessitated excluding them from the immunized series. In the parallel intravenous group the results

would have been equally unsatisfactory had not the animals been killed before regeneration in the involved tubules began.

The results show that with uranium it is not possible to immunize the whole organism but a certain degree of tolerance is attainable. In series "A" this ranges from 16 to 40, and in series "B" from 9 to 40 times the lethal dose.

In my hands the colorimetric method used by Gil y Gil for the quantitative determination of uranium in the urine proved to be unreliable even when known amounts of uranium were added to normal rabbit urine. For some reason, perhaps due to pigments in the urine, such qualitative differences in color developed that accurate readings on the colorimeter were impossible. As has already been stated this method has very definite limitations because most specimens of urine from uranium rabbits contain blood. For these reasons I did not attempt to make colorimetric determinations in any of the immunized animals.

The biological method used by Gil y Gil proved reliable although it was found necessary to inject the urine subcutaneously rather than intraperitoneally since the latter procedure invariably killed the mice within a few minutes or hours. A number of mice were injected with 2 c. c. of sterilized urine from a normal rabbit, allowed to live four or five days, killed and the kidneys sectioned. No lesions were found, indicating that there is nothing in urine itself to injure the kidney. In order to study the localization of uranium in the mouse kidney several animals were given 0.0005 gm. dissolved in 2 ccs. of normal rabbit urine. After four days typical but rather extensive necrosis was found in the proximal convoluted tubules.

To compare the excretion ability of an acutely poisoned kidney with that of a partially immunized one a rabbit was given a subcutaneous injection of 0.009 gm. of uranium and at the same time a like amount was injected in Rabbit 83-A which had had two previous doses (0.001 and 0.003 gm.). The urine from each animal was collected for three days following injection and 2 c. c. from each days specimen administered to mice. The mice receiving urine from the first and second day's specimens of the non-immunized animal showed very slight epithelial damage but on the third day a moderate degree of necrosis was noted. Urine from Rabbit 83-A on the first day produced the same degree of nephritis seen in the acutely poisoned animal on the third day. A positive though slight nephritis was present in the mouse injected with the second day's specimen while that of the third day was negative. This would seem to indicate that even a partially immunized kidney is capable of excreting uranium more rapidly than an acutely poisoned kidney.

Rabbit BAI-B offers more definite proof of rapid excretion of uranium. The mouse given urine collected on the twenty-first day after 0.008 gm., had been given was negative. The rabbit was then given 0.016 gm. of uranium. Urine from the 4, 8, and 22-hour collections produced definite lesions in mice, very marked in the first and moderate in the others. Mice injected with urine from the third, fourth, and fifth days were negative. If we may

judge from the findings in other rabbits in the series dying at this stage, rabbit BAI-B must already have had a fairly well advanced chronic nephritis.

Rabbit 4-A was allowed a rest period of three months following the administration of 0.064 gm. thus offering the opportunity of determining how long an immunized animal would continue to excrete uranium in the urine. A mouse injected with urine from the twenty-first day after 0.032 gm. exhibited well marked uranium lesions. Urine from the first three days after giving 0.064 gm. contained enough uranium to produce extensive and widespread necrosis in the convoluted tubules. Following this the extent of necrosis gradually diminished but was constantly found up to the twenty-fifth day at which time daily injections of urine into mice were discontinued. Urine from the thirtieth and thirty-third days caused slight lesions but that of the thirty-fifth did not. Positive results were obtained with urine from the fortieth and forty-sixth days but were negative for the sixtieth and nintieth. In this rabbit also it is seen that while excretion occurred over a long period of time, the amount, as indicated by the intensity of the damage produced in mice, was much greater in the first three days than at any time thereafter.

This method was used in a number of rabbits besides those mentioned but the results are so similar to those of BAI-B and 4-A that repetition is unnecessary.

As a qualitative test for the presence of uranium in urine the biological method is reliable and apparently quite sensitive but it gives only a rough indication of the quantity excreted. Judging by the extent of kidney damage in mice it would appear that the greater part of the uranium is excreted during the first three days after a given injection but with higher dosages in immunized animals small quantities may be excreted for a considerable length of time.

Potassium ferrocyanide was used as a qualitative test for the presence of uranium in all urines examined. The specimens were diluted with water to weaken the yellowish or brownish color of the urine, acidified with acetic acid and to this was added a few drops of 5 per cent potassium ferrocyanide. It is interesting to note in connection with biological results that a strongly positive test for uranyl ferrocyanide was obtained in the first twenty-four urine from rabbit 4-A after the administration of 0.064 gm. The test was negative in all subsequent specimens. After the injection of 0.08 gm. this animal passed no urine on the first day but the specimen obtained on the second day gave an unmistakably positive test for uranium. The test was weakly positive on the first day after the final dose of 0.096 gm. In rabbits 15, 80, and 81-GyG-J-24 strongly positive reactions for uranium were obtained in the urine passed on the first day after injection of 0.08 gm. but were negative thereafter.

A quantitative method for estimating uranium in body tissues and fluids which appeared to give accurate results in the hands of Karsner, Reimann, and Brooks (46) was next tried. Unfortunately there is some ambiguity in

(46) Karsner, H. T., Reimann, S. P., and Brooks, S. C. Studies of uranium

poisoning. II The solubility of uranium oxide in artificial and human gastric juice. J. Med. Research, 38: p. 163-168, 1918. Ibid, p. 169, III. The question of renal tissue affinity for uranium.

the outline of technical procedure and this led me into an error which was not discovered until too late to rectify. It was found on adding potassium ferrocyanide that iron was still present in the solution titrated. The results were therefore unreliable since iron also oxidizes potassium permanganate and the figures obtained were for both metals.

That considerable uranium was often present in the urine from a number of rabbits having the largest doses I am quite sure. In practicing the method, known quantities of uranium nitrate were added to urine and in the ash after incineration the yellow color of uranium oxide was always visible. In the urine from immunized rabbits this was likewise true in several instances.

The quantitative estimation of uranium excretion might well be made the basis of a separate study.

Schneider (47) working with uranium poisoned Petromyzon fluviatilis

(47) Schneider, G., Ein Beitrag zur Physiologie der Niere niederer Wirbelthiere, Skand. Arch. f. Physiol. 14: p. 383-389, 1903.

found that by using a fixing solution consisting of potassium ferrocyanide, picric acid and HCL, uranyl ferrocyanide was precipitated in the renal epithelium.

This method was tried in both acutely poisoned and immunized rabbits but without positive results. In the regenerated epithelium of two immunized animals an abundance of yellowish-brown granules was found but the appearance is exactly the same in sections stained by ordinary methods so that it is very unlikely that the substance is uranium.

The nature of the pigment so constantly observed in regenerated epithelium is uncertain. It is non-iron containing and therefore cannot be hemosiderin. It may possibly be derived from bits of necrotic cell cytoplasm not infrequently observed in the process of being engulfed by the new epithelial elements although I have never observed an intermediate stage between the pink-staining masses and the yellowish-brown pigment.

If the liver is damaged by uranium one would expect some histological change in the cells and with this possibility in mind I have studied this organ routinely along with the kidney. In the acutely poisoned animals after small doses nothing was found. As the dosage in immunized animals was increased some constant and very striking changes were observed. In animals of series "A" dying or killed after the administration of 0.064 gm. of uranium a slight but definite fatty degenerative infiltration was noted. In one animals (6-A) living fourteen days after injection of 0.064 gm. this was very slight, possibly indicating that the change is transitory. All rabbits succumbing from the effects of 0.08 or 0.081 gm. had well marked fatty change diffusely in the lobules but still most marked toward the central veins. Those dying after 0.096 gm. exhibited extreme fatty degenerative infiltration involving the entire lobules with the exception of a thin rim of cells about

the portal veins. The liver in these animals grossly appeared yellowish, very friable and distinctly fatty.

In the intravenous series, with the exception of one animal in which a slight degree of fatty change occurred after giving 0.016 gm., fat was detected only after 0.032 gm. had been given. One rabbit which lived for 20 days after a dose of 0.032 gm. showed no fat in the liver. In rabbits given 0.04 or more grams the fatty degenerative infiltration was comparable in extent with 0.08 and 0.096 gm. in the subcutaneous series. In every instance specific fat stains were made to check the findings. Very little actual necrosis was visible in the hepatic cells and evidences of cellular regeneration were never found. The significance of these changes is debatable. Fatty changes are known to occur in the presence of many toxic and metabolic disturbances and it is possible that this alone is sufficient to account for the liver damage. The only certain way of settling the question is by quantitative estimation. This was attempted but the same difficulty of freeing from iron previously mentioned was encountered and the results were inconclusive.

Even if uranium is taken up by the liver the fact of immunity on the part of renal tubular epithelium is not disproven since it has been shown that even after the largest doses of uranium the kidney is still able to excrete the metal in sufficient quantity to give positive qualitative and biological tests.

After having demonstrated the fact of immunity it appeared desirable to determine whether this is transitory or more or less permanent.

Rabbit 4-A after receiving 0.064 gm. was allowed a three-months rest period after which the next regular increase in dosage, 0.08 gm. was administered. During the rest period the animal gained 450 gms. and was to all external appearances a healthy rabbit. Following 0.08 gm. the animal reacted fully as well as others allowed the usual three-week period between injections.

In series "B," rabbits BCI, BEI and BGI were chosen quite at random from others at the same stage of immunization and no further injections were given for nine weeks. During this interval all gained slightly in weight and appeared well and lively. At the end of the rest period all received 0.024 gm. Following this dose the animals were quite sick but survived and the doses were later increased in the regular manner. BGI in the end showed the greatest tolerance in the intravenous series.

The series is too small to draw definite conclusions as to the permanency of the immunity but so far as they go indicate that immunity is retained for an appreciable length of time.

Summary.

Uranium nitrate produces in the rabbit a glomerulotubular nephritis which in the chronic stages resembles that seen in the human. It is true that tubular lesions are more prominent than glomerular in all stages of the disease but some alteration in the latter will be found in all instances.

Repair begins early in the epithelium of the tufts and Bowman's membrane. Frequently the number of new cells is excessive and leads to the formation of epithelial crescents and even complete obliteration of the capsular

space, glomerular atrophy and hyaline degeneration. In the chronic stage it is rare indeed not to find at least some proliferation of Bowman's epithelium. In other instances the capsular space is dilated and cystic with atrophy of the accompanying glomerulus. In even the most markedly scarred kidneys there are always some hypertrophic and apparently functioning glomeruli.

The same glomerular lesions Baehr (32) produced by intra-arterial injection of very small quantities may be brought about by repeated and increased doses administered either intravenously or subcutaneously.

The regenerative capacity of renal tubular epithelium after injury by uranium is remarkable, particularly when the doses are so graduated that not all cells are killed at one time and when sufficient time is allowed between injections for complete restoration.

Proof of Immunity.

1. It has been shown by experiments on normal rabbits that 0.001 gm. of uranium administered subcutaneously or half this quantity intravenously, will produce unmistakable histological evidences of injury in the glomeruli and epithelium of the distal and transitional segments of the proximal convoluted tubules. In the glomeruli these changes are swelling and desquamation of epithelial cells, diapedesis or hemorrhage into the capsular space, intraglomerular hemorrhages, and hyaline droplet degeneration while in the tubules there is complete necrosis of cells.

2. If subsequently larger quantities than are known to produce these lesions can be administered without evidence of damage it may fairly be assumed that the glomeruli and regenerated tubules have acquired an immunity for the injurious agent, providing it can be proven that the poison still comes in contact with these structures.

3. That uranium still passes through the kidney with chronic injury is shown of the proximal convoluted tubules by necrosis of epithelium in segments of the proximal convoluted tubules which are not injured until large amounts of the metal are given.

4. Intravital staining of the chronic uranium kidney with carmine proves that many glomeruli and regenerated tubules are still functioning. It is not unreasonable to suppose that uranium reaches the same structures as the dye.

5. The biological and qualitative tests on the urine from immunized rabbits prove conclusively that these animals are capable of excreting uranium both rapidly and in considerable amounts.

6. Numerous rabbits have been given both subcutaneous and intravenous doses of uranium from 54 to 96 times greater than the quantity known to produce glomerular and tubular damage in a normal animal yet without evidence of injury being shown.

Mechanism of the Immunity.

Experiments with mice show that although sufficient uranium is excreted in the urine of rabbits on the first and second days of the acute stage to produce slight kidney lesions in mice it is not until the third day that enough is present to evoke much of a nephritis. The rate of excretion is in inverse proportion to that of partially or fully immunized animals. Why is little or no uranium excreted by the acutely dam-

aged kidney while the immunized organ permits its ready passage? The most plausible explanation lies in the action of the salts of heavy metals. It is well known that these salts, including uranium, precipitate proteins and form metallic salts of albumins (albuminates). Unless a very large quantity of uranium is administered it would appear that there is sufficient protein in the susceptible parts of the kidney apparatus to combine and fix the poison so that little or none will be excreted in the urine until the dead cells (uranium albuminate) become detached and washed out of the kidney. Microscopic examination of the kidney and urine shows that after two or three days many cells in the renal tubules have already been fused into casts and will also be found in the urine. This would explain the appearance of the more marked nephritis in mice given urine on the third day after injection of a non-immunized rabbit.

In the immunized kidney on the other hand little original epithelium remains in the susceptible parts of the tubules. By gradually increasing the doses of uranium the greater part of the original epithelium has been destroyed and replaced by vastly different appearing cells in which no histological evidence of injury is to be found. Such kidneys in contrast to acutely poisoned organs allow uranium in appreciable quantities to pass through into the urine.

Two possible explanations for the failure of the poison to injure the regenerated cells are offered: (1) The chronic uranium kidney is unable to excrete uranium, (2) the regenerated epithelium has acquired an immunity for the poison.

The first is readily disposed of since it has already been shown that uranium is excreted.

The most logical explanation of the mechanism of the immunity is to assume that the regenerated epithelium is able to prevent the poison from uniting with the cell protein. In this event it would be expected that the injurious substance would be excreted in the urine, and such is the case. Another possible explanation is that the new cells are capable of taking up the poison and detoxicating it, but the amount excreted in the urine and the failure to find the metal in the epithelium by the use of a specific fixative makes this improbable.

In conclusion the author wishes to express his gratitude and appreciation to Dr. A. S. Warthin and Dr. C. V. Weller under whose friendly guidance this work has been carried out.

Heart Strain and Its Consequences*

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THE subject of mechanical strain of the heart and great vessels has been considered in its clinical aspects in the medical literature since the middle of the nineteenth century. Following the pioneer work of Peacock, da Costa, Traube, Seitz, and Allbutt and Roy, the condition became recognized as a clinical entity. To Allbutt the greatest credit is, perhaps, due for describing a large number of cases, clearly demonstrating the operation of overwork and stress in the production of cardiac diseases—factors that had previously been overlooked or neglected by pathologists. The opportunities afforded in modern industry for the study of this subject have still further elaborated our conceptions of heart strain, at the same time verifying the opinions held by the great clinicians.

Of recent years, the subject has assumed increasing importance. The advent of compensation laws in England, Germany and the United States has been a great stimulus to the analysis of the medical aspects of this subject. The broad and considerate interpretation of the law, especially by the English courts, has redefined the terms "accident" and "injury," "disability" and "compensation," so that whatever injurious happens to an individual during work must be considered in its relation to the occupation.

The effect of strain upon the heart is now beginning to receive a revived interest also, since our attention has been focussed, during the past decade, upon the increasing prevalence and economic significance of heart disease in general.

Definition

Heart strain is an organic condition associated with the sudden development of symptoms, referable to the heart and aorta, which can be attributed to some unusual muscular effort or overexertion, and which results in physical disability of varying degree and duration. The emphasis is placed upon the subjective complaints of the patient, because they are the outstanding features which bring the condition to our notice. It is the sequence of cardiac symptoms following effort that gives the clinical picture its individual character.

Etiology

Strain of the Healthy Heart.—Like disease, health is also a relative term. In harmony with the liberal interpre-

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tation of the compensation laws, we must assume for practical purposes that strain of the healthy heart is possible. This implies the acceptance of the generalization that the heart is healthy, from a labor standpoint, if a man is able for a long period to pursue his strenuous occupation without distress and without long periods of absence from work.

It must be emphasized that, regarding the safety of the heart, physical training, which has its beneficial effects upon the circulation, is of the first importance as a preventive against cardiac strain. A person properly trained in the laborious manoeuvres of his occupation and the postural leverage to be used need not fear cardiac strain as much as one unaccustomed to the labor.

Athletes who make violent efforts for shorter or longer periods allow plenty of time for the heart to recover in the intervals. However, the observations made in athletes indicate that prolonged overexertion, even in the trained individual, may affect the heart. Feats of strength and endurance cannot fail, sooner or later, to leave their marks upon the respiratory and circulatory systems. Among the most notable causes of strain in athletes are rowing, running, and fast bicycle riding. Thus, in one Marathon race, the leading runner collapsed in the last quarter-mile with an extremely enlarged heart as a result of the exertion. The hearts were also dilated in the second and third winners in the same race. An English Rugby International suddenly collapsed during a match. So also did a young professional football player at the beginning of the season after vigorous exertion in the practice games. His heart was dilated or hypertrophied to five inches to the left of the midline of the sternum before the game in which he broke down. In some circumstances, a single feat of violent exertion may be followed not only by prolonged, or even permanent, inability to take exercise, but also by pathological dilatation of the heart or other signs of myocardial defect.

Heart strain may therefore be fully explained as being the outcome of extreme or prolonged exertion, with resulting diminished contractile power. It will come on earlier when there has been some pre-existing abnormal condition, such as increased blood pressure, or when the heart is not mature—as in young adolescents who do too vigorous exercise.

Occupation.—As long as human effort is utilized to drag, lift, pull, or push weights that should be relegated to mechanical apparatus, there will inevitably be disastrous effects upon the human organism in consequence of strain. This applies to all occupations where effort of this nature is demanded. With the changing conditions and enlightenment in the industries, it will apply more to some occupations than to others. It will take its human toll inevitably until it becomes recognized that the power of muscles in the human machine must not be stressed to the extreme. There is an exacting compulsion of labor in industry without sufficient regard to the conservation of the energy of the individual, especially in certain occupations. Thus forgemen, rivetters, hodmen, stone masons, sailors, soldiers,

longshoremen, blacksmiths, porters, metal workers, and miners are still compelled to exert great and often sudden and violent effort while at work.

The part of stress in the causation even of chronic cardio-arterial diseases comes out plainly when such cases are considered in numbers large enough. When, for instance, large numbers of persons engaged in laborious callings are contrasted with large numbers of those whose pursuits are mechanically less urgent, a predominating excess of cardiovascular involvement in the laborers is found. As an occupational effect, therefore, chronic cardiac disease is most frequent among these classes of workers.

In the production of acute or primary cardiac strain, however, the occupation of the individual is not of material importance. The heart of a man engaged in strenuous labor is enabled by adjustment to support rather severe physical exertion. Similar, or even milder sudden exertion in a man unaccustomed to it, is likely to produce heart strain.

Of fifteen cases of primary heart strain recently examined by us, the occupations were given as follows: Laborers 4; helpers on truck 2; mechanic's helper 1; mechanic on wind organs 1; porter 1; shipping clerk 1; iron worker 1; electrical worker 1; plumber's laborer 1; janitor 1; driver 1.

For years a man may pursue a laborious occupation without any apparent ill effects. But on one particular occasion, such as lifting a heavy case in an uncomfortable or unusual posture, acute heart strain will develop. It is impossible, of course, in such cases to evaluate the predisposing effects of the continual duress of labor. The condition of acute primary strain must always be considered an accidental occurrence, and stress of occupation must be accepted simply as a predisposing etiological factor.

Chronic Infections and Intoxications.—Attacks of an infection, manifestly or insidiously, often so impair the cardiac muscle and so reduce its resiliency as to render it liable to yield prematurely or unexpectedly to overwork, with consequent strain. Chronic stress is so intimately confused with toxic factors, that it is often exceedingly difficult or even impossible to distribute its due weight to each of these several causes.

Chronic alcoholism, tobacco, and venereal disease, are unquestionably very important contributory causes of heart strain. They produce effects, usually of a degenerative nature upon the heart muscle.

The dilatation of the heart in severe and prolonged anemia, as well as that which occurs after acute illness, must also be considered a form of heart strain. Other factors, sheer fatigue, infections more or less latent, sudden emotion or prolonged grief, insufficiency of sleep, the worries of lessons, puberty, inherited nervousness, excess of venery, and other such incidents also predispose to strain.

Exercise, therefore, though not severe enough to be injurious to a healthy heart, may actually strain a heart whose nutritive condition has become less than normal.

Previously Existing Heart Disease.—Unusual exertion may reveal a lat-

ent defect in a heart which under ordinary circumstances, or for some time at any rate, would have passed as sound. In men of middle age, a breakdown of the heart is often thus acutely determined; but in later life it is usually very difficult to distinguish between lesions due mainly to variations of stress and resistance, and those due to the tooth of time.

Pre-existing heart disease is often discovered at the time complaint is made of the symptoms developing during work. The forms of heart disease thus discovered usually fall into the classical valvular and myocardial conditions, presenting the typical signs. Upon close questioning and careful investigation, there may also be discovered the usual etiological factor of a previous acute infection. Tonsillitis and rheumatism are particularly conspicuous among the causes, and often a history of tonsillectomy or a stay in a hospital for rheumatic infection is part of the past history. Given these previously existing heart conditions, we must eliminate those signs which can be attributed to them, before considering the superimposed effects of any strain upon the heart. Overexertion will, however, at times produce precordial pain which previously was not felt to any marked degree in a heart already diseased, and may induce changes in the heart rate as well as initiate disturbances which lead directly to cardiac failure. In these cases, therefore, the question of aggravation of a previously existent heart condition must be considered.

Age.—In patients over forty years of age, it is usual to find a degree of substitution of fibrous for elastic tissue in the aorta with consequently lessened elasticity of the wall. If this is exceeded by some unusual exertion in lifting or pulling, the resulting strain on the aorta and heart may be irreparable. It is in this period of life that the aorta and ventricle are especially liable to permanent injury due to strain.

Sex.—It is natural to expect males rather than females to develop heart strain in industries, because of the greater liability of the former to sudden physical exertion. Cases of heart strain and consequent cardiac pain in women who have undertaken sudden physical stress in their homes, however, are known. A case of rupture of the aorta in a healthy woman has been recorded during the pains of labor and childbirth.

Exciting Cause of Heart Strain.—Excessive exertion such as is entailed in sudden lifting, pulling, pushing, straining, stair or mountain climbing, especially supporting a load, etc. is the only exciting factor in the production of acute primary heart strain.

To illustrate from our series of cases the uniform importance of the exciting cause of heart strain, the patients' statements are given:

> During severe straining in a difficult and uncomfortable posture to push up a case weighing 100-120 lb., suddenly became unconscious, and on awakening had severe pain in the heart.
>
> While lifting the end of an iron railing weighing about 1500 lb., suddenly felt a severe sharp shooting pain from the right upper abdomen up to the left pectoral region.

While lifting a transformer weighing about 150 lbs., felt a sudden sharp knife-like pain from the shoulder down to the costal margin.

While carrying a bag of sugar weighing 100 lbs. up one flight of stairs, felt a tearing pain in the region below the left breast.

While supporting and carrying an iron pipe 40 inches in diameter and 29 feet long, felt slight pain and soreness from the left shoulder down to below the breast.

While pulling a very heavy organ, was suddenly seized by a very severe sharp pain in the left breast region.

While lifting a very heavy stone, felt as if something were tearing in the lower sternal region.

While lifting an ice box, felt sudden sharp knife-like pain in the left lower chest.

During a fire, tried to pull apart the iron bars across the windows of the room in which he was trapped, and following the accident was extremely dyspneic with sticking pain in the region of the heart.

Mechanics of the Circulation in Heart Strain

Although the machinery of the circulation allows for a rather wide field of responsiveness to effort, there are definite limits beyond which any attempt on the part of the heart and aorta to maintain adequate circulation is organically injurious to these tissues. The normal heart naturally adapts itself to those stresses which, in various degrees, all have to encounter. We must, however, be able to recognize the signs of any overstepping of the normal limits of the heart's responsiveness.

The various effects of stress upon the heart may be considered with regard to the amount of the stress, the frequency of repetition or intermittence of the stress, the time allowed for rest and recovery, and the previous training of the heart to receive the stress to which it is exposed. These aspects are particularly apposite when practically considered from an industrial standpoint.

It is mainly in the laborious industries that strain affects persons of otherwise healthy body. By a single or persistent muscular effort the organs of the circulation may be urged to a menacing or hurtful degree. Efforts of less severity may tell upon a vascular system already somewhat impaired by other causes. Thus, if we assume a trained man to be working continuously with his muscles at a uniform but moderate rate, the total daily blood pressure in his arteries would not be above the mean of that of people in light occupations. If we assume the same man to carry a load up a flight of steps every ten minutes—although still the mean of his blood pressures and cardiac output for 24 hours may not be excessive, the maximum pressure, that is, the initial rise at the outset of each effort, may be very high.

Again, if we take another man, one who does not carry loads hour by hour and day by day, but who takes a load up occasionally—in him the maximal arterial pressure, as he shoulders the load will be driven much higher than under the same effort more regularly undertaken by, for example, a porter whose thoracic capacity, blood volume,

and vascular distributions are accustomed to such recurrent stresses. And if a clerk or one in a sedentary occupation were to shoulder a load, his defect in the automatic adaptations to such exercise might cause so sudden and relatively so great an increase of arterial pressure as to embarrass, to dilate, and even to strain his heart; possibly indeed to rupture some part of it.

"Tone" is used to express the amount of energy which heart muscle fibres can develop during systole. Since stretching in a rather wide measure increases the contractile power or tone of the heart muscle fibres, the heart under stress dilates. With further dilatation, as in fatigue, the tone lessens. The muscle fibres completely recover, however, without any persisting organic change.

With heart strain, there occurs an actual stretching of the muscle fibres beyond the limits of their elasticity. Strain, then implies a permanent change in the intracellular and interfibrillar structure. The loss of tone in heart strain is due to an organic change and complete recovery is impossible. If the heart after strain cannot maintain the output necessary during rest, it dilates gradually, and under its steady pressure the pericardium also will give way and the condition becomes irremediable.

It appears probable then that the principles which underlie the working of the normal heart also hold good for the behavior of the heart during overstress. As long as the fibres of the heart or aorta have not been mechanically stretched beyond the limits of their elasticity, heart strain cannot be said to have occurred.

Pathology

Heart strain, from a pathological standpoint, is the effect of stress or reiterated stresses upon heart muscle with resultant stretching of the fibres beyond their elastic limits. The occurrence of the particulate alteration in muscle fibres as a result of mechanical stress is obviously very difficult either to prove or to disprove pathologically. But the pathological dilatation of the heart which may occur, clearly implies the existence of some structural change in the heart muscle, which interferes with the normal transformations of energy, of which visible contraction is the outward sign. The suggestion that strain of the muscle fibres, by permanently altering their elastic state, allows the heart passively to dilate to excess, appears to provide an adequate explanation of the dilatation; and at the same time places it in the category of pathological rather than physiological dilatation.

It is relatively seldom that pathological examination of the heart can be made promptly after it has endured acute strain. The opportunity arises when the strain has caused prompt supervening death. In such cases, there is found partial or complete rupture of the heart or aorta at the site of pre-existing aneurysm or extensive degeneration in either location.

Postmortem pathological findings in a case that has shown symptoms of heart strain some years before death cannot be adjudicated with any precision to the various factors involved in producing the lesions found. However, certain morbid processes are at-

tributable to previously existing diseases; others, particularly in the vessels, to previous deterioration as a result of chronic stress; while still other lesions may be considered, by exclusion, the result of the acute strain under our consideration.

Pathological lesions in the heart and aorta which have undergone strain can therefore be classified as follows:

1. Previously existing cardiovascular lesions due to antecedent acute or chronic infections, intoxications, and senescence.

2. Gradual deterioration of the vascular system due to hard muscular labor during long terms of years, especially in middle age.

3. Disease of the aortic area and valves produced by sudden stress or extraordinary effort—the result of acute heart strain.

4. Injury to the heart muscle resulting from the same cause.

This classification distinguishes acute strains from chronic; the effect, that is, of some instant or brief stress upon the heart from the deferred effects of protracted labors. It also distinguishes injuries of the valves from those which in the first instance affect the walls of the heart.

Diseases of the Aortic Area of the Heart—Syphilis, anemia, chronic alcoholism, gout, lead poisoning, as well as the processes and products of senescence are conducive to the degenerative changes which invade the aortic region of the heart. Connective tissue fibre, when substituted for muscular fibre, as we find commonly in old hearts, gives to the part a higher resistance but at the cost of resilience; so that once overstressed this fibre never recovers its former condition.

Hypertrophy—Hypertrophy of the left ventricle is a consequence of exertion in consonance with the recognized compensatory capacity of muscular structures in the body. It is to be regarded simply as the static expression of increased function, or of a larger contraction volume. This hypertrophy may be transitory or more or less permanent. In either case it produces an effect on the associated parts. The line between the aortic area of the heart and the aorta itself being no barrier to the extension of disease, the aorta dilates; its elasticity is impaired; its walls are diseased; and the coronary arteries become themselves less pervious or are blocked at their orifices.

Coronary Disease—A grave feature of atheromatous degeneration is that these changes involve, sooner or later, the orifices of the coronary arteries. From the first, perhaps, these arteries, like the rest of the aortic area, suffer under excessive percussion and the extreme variations of pressure. A hypertrophied ventricle, which is usually present in these cases, may at first be able to supply the increased nutrition which its greater work demands. With coronary involvement, however, the heart will receive by this route considerably less than its normal nourishment.

Notwithstanding this deprivation, the hypertrophied muscle sometimes retains a fair degree of functional value in a person of comparative inactivity. This is probably explained by the very slow progress of the lesion

allowing for re-adaptation of the heart.

Cardiac Dilatation—Dilatation of the heart is due to continuously excessive aortic pressure. Allbutt indicates that there are three modes of dilatation: active adaptive physiological dilatation to receive large volumes of blood; passive but remediable dilatation with abatement of tone or more gradual fatigue; and the irremediable atonic dilatation due to acute primary heart strain.

When the ventricle opens to receive the larger loads of blood there need not be any loss of tone. The cavity, by some vital endowment enlarges to receive the excessive quantum without any rise of intraventricular pressure. This is what occurs in chronic valvular lesions. In disease, as compared with experiment, we have the important factor of time and of changes gradual enough to allow of re-adaptation. When in acute strain, tone of some fibres begins to fail atonic dilatation supervenes.

In cases of death following acute strain, the cavities of the heart are usually dilated and the muscular walls frequently show a certain amount of antecedent hypertrophy with or without degeneration.

Rupture of the Aortic Valve—It is well known that sudden effort is capable of producing rupture of the aortic semilunar cusps. In the old experiments of Potain on the cadaver, a pressure of 300 mm. of mercury in the aorta was shown to be injurious to the aortic valves. Marey found that the intrathoracic pressure after effort often rose to this height in the large arterial trunks. The sudden increase of pressure following effort in individuals whose usual level of pressure is already high is even more marked, and such individuals are more likely to suffer aortic valvular rupture.

Aortic insufficiency due to muscular strain is divisible into three classes: a few cases of sudden rupture of a healthy valve and sound aorta; cases of sudden rupture of a valve previously impaired by some local lesion or general disease; and cases of insidious forcing of the valve by the importunity of repeated muscular stress, probably with valvulitis.

It must be reasoned that if a certain amount of effort can be the exciting cause in producing acute heart strain in a predisposed heart, a greater stress may produce a lesion in an anatomically intact heart. Thus muscular exertion, very sudden or excessive, and attended perhaps by fixation of the chest walls with arrest of breathing, may produce direct rupture of a cusp of the aortic valve. The occurrence is not necessarily occupational. We recently observed its development following an effort to swim made by a plethoric man of 50, with hypertension.

One or more of the cusps may be torn; the posterior cusp is said to be the most frequently injured. A cusp may split from the free border across, or it may be torn at the base from its attachment. In one case an aortic cusp was forced inwards, and a pouch driven out from the wall of the aorta above it.

Rupture of the Aorta or Heart—The possibility of rupture of a healthy aorta under strain is mooted academically, though a good many reported cases seem to answer this question in

the affirmative. In general, the age incidence of spontaneous rupture of the aorta is widespread, indicating no uniform etiological factor. Thus, in a patient of Allbutt's, a very healthy boy aged 13, rupture of the aorta took place a little above one of the cusps of the valve during very severe exertion. In several cases, there was found very little pre-existing disease in the region of the rupture, while in a larger number there were present unmistakable signs of luetic or arteriosclerotic disease, or pre-existing dissecting aneurysm. In all cases, the sudden increase of blood pressure during work was the exciting cause in producing the rupture.

From experiments on animals it seems that on suddenly produced insufficiency of the aortic valve, the aortic pressure may be so great as even to rupture the unprepared ventricle. In one such case reported, there occurred also sudden rupture of the posterior pillar of the lower mitral cusp. It is almost certain, as was maintained by Morgagni, that a rupture never occurs in a sound heart muscle.

In the etiology of rupture of the heart, coronary sclerosis holds a preeminent place. In consequence there develops ischemic necrosis with thinning and replacement fibrosis and the formation of aneurysm of the left ventricle due to the high intraventricular pressure. Fatty infiltration of the heart muscle or brown atrophy due to the slow coronary scerlosis of age may exist. In all these cases, the sudden increase of blood pressure during work plays a critical role in precipitating the rupture of the heart.

The pathological conditions found may be tabulated as the chronic effects of prolonged stress and the effects of acute strain as follows:

I. Effects of Chronic Stress
1. Atheroma of the aorta and arteriosclerosis
2. Hypertrophy of the heart
3. Cardiac dilatation
4. Coronary artery disease
5. Aneurysm of the left ventricle
6. Aneurysm of the aorta
7. Temporary diminution of tone or contractile power of the heart, as after fatigue.

II. Effects of Acute Heart Strain.
1. Stretching of fibres beyond their elasticity, or dissarrangement of organic relation between fibres.
2. Tearing of fibres in the aorta or the heart wall.
3. Rupture of aortic semilunar cusp
4. Rupture of aorta or aortic aneurysm
5. Rupture of the heart or an aneurysm of the ventricle.

Symptoms of Acute Heart Strain

Onset—Characteristically, the symptoms of acute heart strain arise during or almost immediately after the performance of some strenuous work. The organic lesion is brought on at the time of greatest cardiac stress and maximal aortic pressure, and these are at their highest during the period of exertion. When no symptoms develop immediately, the diagnosis of acute heart strain is not tenable. If the lesion remains for a time asymptomatic, it must be considered an effect of chronic stress. As closely as pos-

sible this principle of the immediate succession of symptoms following effort should be adhered to in determining the causal bearing of the particular muscular feat upon the subsequent disability.

Pain—Pain over the region of the heart or behind the sternum is usually the first development in cases of heart strain. It is characteristically severe, often of a tearing nature, but sometimes sore, aching, knife-like, shooting or burning in character. Or, it may be typically anginal with a sense of constriction across the chest. It is usually localized below the left breast, or may radiate down from the shoulder to the left costal margin, or to the right of the sternum, or down the left arm. It may be severe enough to double the patient over in distress, or for a while be felt merely as a numbness or oppression in the chest.

The significant features about the pain are its close relation in point of time to the muscular effort, and its persistence, or subsequent recurrence after further exertion. If the patient becomes unconscious with the immediate strain, the pain is felt as soon as he recovers consciousness.

Weakness—With the pain, there is a sense of weakness which immediately disables the patient from resuming any strenuous work. It may be extreme enough to compel him to sit down or lie down wherever he may be, with a feeling of faintness even on the slightest motion. There may be dizziness and a sensation of darkness before the eyes, and buzzing in the ears. The onset may occur with sudden unconsciousness, the patient falling in collapse when the effort has been extreme. He may faint after a varying period of rest, when he again attempts work.

Dyspnea and Palpitation—Associated with the pain and sense of constriction or burning in the chest, there is usually marked shortness of breath. This may appear as an actual gasping for breath which sometimes becomes alarming. It may last for a long time or be more or less temporary with the onset, and recur under the stress of renewed activity. Later, in severe cases, it may become manifestly of the type of cardiac asthma with nocturnal distress, the patient suddenly compelled to sit up breathless for a time.

Palpitation is often felt simultaneously with the occurrence of heart strain. Often there is a marked irregularity due to premature beats. This is exaggerated by effort, such as attempting any work or even walking a moderate distance.

Disability—A certain degree of disability and limitation of the field of cardiac response is a cardinal symptom of heart strain. The patient is unable to support any exertion without some degree of distress, pain, dyspnea, palpitation and weakness. While at rest, however, he may be quite comfortable.

Heart Failure—In the more severe cases, or in patients who make an effort to continue their work, dyspnea, edema of the legs and other symptoms of heart failure ensue. They are a prompt sequel to rupture of an aortic cusp. Extreme orthopnea or cardiac asthma, and cough may develop due to congestion of the lungs. In most cases, however, these symptoms develop an uncertain number of years after the occurrence of primary heart strain.

Death From Primary Heart Strain—Sudden death may occur during or immediately after the performance of extremely severe muscular effort. When this happens, the circulatory system was disposed to a fatal injury by pre-existing disease or weakness which impaired the heart's efficiency. Rupture of an aortic aneurysm or of the heart itself is the usual reason for sudden death due to strain, and death may be delayed even for a few days after this event in rare cases. Due to severe pain alone, death may occur after the onset of heart strain from reflex stimulation of the vagus and cardiac inhibition.

Physical Signs

Immediately after the occurrence of heart strain the physical signs will vary from the very slight and equivocal ones of simple tachycardia to those of collapse with great cardiac disturbance, and will depend upon the lesion caused by the strain. The pulse is usually small, feeble and rapid. It is frequently irregular with premature beats, and occasionally very rapid as in an attack of paroxysmal tachycardia. With the progress of time, the area of cardiac dulness becomes enlarged and the sounds may be indistinct and feeble or short and sharp. This, of course, indicates a severe affection. In milder cases, the signs gradually disappear, and the heart becomes apparently normal.

After exertion, the pulse rate quickens and there is manifest shortness of breath. In a large number of cases there is heard a roughened murmur over the apex and aortic area as evidence of an atheromatous change that may have existed prior to the injury.

Tender spots on the chest wall in heart strain are an important and significant sign in these cases, closely related to the complaint of pain. Several tender spots may be elicited usually localized over the ribs in the region of the heart apex or the precordium. These tender areas on the chest wall have a practical clinical value in diagnosis.

Although pulsus alternans occurs only in the very severe cases, the polygraphic tracings will occasionally reveal it when otherwise it might be overlooked. The blood pressure varies and is usually somewhat elevated, both systolic and diastolic.

The electrocardiogram indicates left ventricular predominance. It may show myocardial changes by inversion of the T wave in any of the leads; and in a few cases, intraventricular heart block may indicate myocardial injury.

The vital capacity in these cases is reduced—sometimes only slightly, but with a severe assault, considerably.

It will thus be seen that there are no characteristic features in the physical diagnosis of heart strain. The signs vary with the previously existing heart condition and with the lesion due to the strain.

Differential Diagnosis

In as much as the physical signs of heart strain are not very definitive, no exact conclusions can be reached by considering these alone. When, however, the symptoms and etiologic history are consistent and the physical signs are suggestive and not contradictory, the patient must be given the benefit of the doubt as to disability from strain of the heart.

It is our duty, however, in cases of

alleged heart strain to differentiate between that and other painful affections of the heart. In many cases, it is also necessary to exclude any other condition which will produce the weakness and other distressing symptoms that may have existed prior to an alleged overstress. Irritable heart often gives physical signs which are suggestive; and, in fact, sometimes this condition is the consequence of heart strain. Injury or strain of the pectoral and skeletal muscles must not be interpreted as cardiac in origin. Pain of a reflex, neuralgic nature must also be excluded.

We have therefore to consider not one aspect alone in this condition, but we must weigh in the balance the entire clinical picture, including the etiological factors, the clinical symptoms and the physical signs indicating cardiac change and disability.

Prognosis

Heart strain of whatever degree must not be dismissed lightly because in point of time, it is a long enduring condition. The prognosis depends upon the severity of the strain and type of cardiac lesion produced. In general, improvement does not take place sufficiently to enable the claimant to resume a strenuous occupation. The healing processes in such a mobile organ as the heart are very slow. The symptoms persist for an indefinite period and, with strenuous exertion, may be aggravated. Extrasystoles may recur under the provocation of slight muscular exertion.

A period of one year may be assumed for practically total disability during which time the patient must rest completely. Another year is allowed for partial disability, during which time the patient will be able to do light work. In the more severe cases, the disability may be a total permanent one. In the less severe cases, it may be a partial permanent one. In the milder cases, the patient may be able to resume his work after a year or two. It is difficult to prognosticate in more definite terms.

In arriving at an opinion as to whether a patient is or is not able to work, the gross physical signs alone are often inadequate criteria. The duration of the symptoms cannot be predicted. The forecast should incline toward allowing a long time for recovery to take place. The patient's youth and length of abstinence from work are favorable factors in the prognosis. The prognosis will also depend upon whether the heart was previously sound or not.

Treatment

For the often severe symptoms of onset of heart strain, the treatment must be symptomatic and stimulating. The patient must be put to bed, his clothes removed, with cold applications to the heart and venesection if there is venous congestion. The acute dyspnea and collapse require stimulants, brandy or coffee, hot baths and mustard pastes applied to chest and back of neck. An intravenous injection of some preparation of digitalis is often marvelous in its effects; it can be followed by subcutaneous injection of some digitalis preparation and epinephrine. Even if the patient rapidly recuperates, complete rest should be enforced as long as possible. Signs of dilatation and a persistently rapid

pulse call for extreme caution and avoidance of all physical exertion.

For the sake of emphasis, the subsequent treatment might almost be summed up in one word—prolonged rest. Some weeks or months are none too long in a mild case for complete physical and mental repose. In general, a period of one year should be allowed for total disability during which time the patient remains under medical supervision and and takes as much rest as possible.

This must, of course, be supplemented by general hygienic measures that are so necessary in the processes of cardiac repair. Moderate doses of digitalis are a great aid in restoring the tonicity of the heart muscle. The time for return to work is indicated in the prognosis above. It may require several years before a patient can resume even ordinary activity. The return from complete rest to full activity must be made very gradually. Light manual work, as sitting at a table without strain or exertion, may be done some months after the accident. The patient can then continue with moderate work such as does not entail heavy lifting, climbing, or strenuous exertion. Often, however, the disability remains total and permanent. This will be best illustrated by the cases appended to this report.

What can be accomplished by care and prolonged treatment is shown by the remarkable results obtained by da Costa in many very severe cases among Union soldiers of the Civil War. Many of these were again able to perform strenuous work and lead active lives after suffering heart-strain.

Heart Strain and Compensation Claims

In relation to hear strain, "accident", in the meaning of the Compensation Law is held to include some unexpected or unforeseen occurrence of physical or physiological nature arising out of and in the course of workman's employment, which produces a disabling heart condition; aggravates a pre-existing heart condition; or causes sudden cardiac death.

From a compensation standpoint, the previous existence of asymptomatic lesions predisposing to the development of heart strain is immaterial. As an accidental development the liability for the sudden disability of the patient falls upon the acute stress or the immediate exciting cause.

It is very necessary to establish certain criteria and principles upon which the basis of judgment in any particular case must depend. These have to be made sufficiently broad to include all cases in which the causal relationship between the accident and the injury is evident, and yet concise enough to permit of no question in any case that may arise.

Several criteria serve to form a clear cut differentiation in analyzing a particular case:

1. Immediate onset after exertion with
2. Symptoms of cardiac disease.
3. Pain
4. Immediate disability
5. Physical findings.

First—The onset of acute heart strain is sudden, immediately following excessive exertion. It is a common but satisfying fallacy on the part of lay people to trace an ailment to a

long antecedent cause. Unless symptoms of heart strain are immediately consequent on the alleged accident, a causal relationship cannot be recognized.

Second—Symptoms of a cardiac affection develop immediately, varying from a degree of faintness, momentary dizziness with pallor, to collapse with profuse cold sweat and even unconsciousness. Dyspnea and palpitation may be very conspicuous and the occurrence of irregular heart beats give a sensation of smothering or of a lump in the throat.

Third—In all cases, immediate pain referable to the heart or aorta is a prominent complaint. This may be extremely severe and persistent.

Fourth—The same exertion as previously endured in the occupation cannot be immediately undertaken. The patient prefers to rest or may do very light work, but finds even that fatiguing. An attempt may be made to resume or continue the routine work, as is only too natural, but strenuous exertion is found to produce distressing symptoms and cannot be continued.

Fifth—The suggestive physical signs are discussed above.

Case Reports

Case 1.—William B., a strong negro porter 52 years old, worked at his occupation for twenty-six years. While piling up cases weighing 100-120 lb. each, after severe straining in a difficult and uncomfortable posture, he suddenly became unconscious. He does not know what followed. Immediately on arousing, he felt a sharp, sticking, continuous pain localized in the xyphoid region; he was extremely pale and had a cold sweat. He felt as if dying, was very weak and dizzy, and completely exhausted; he was unable to stand up, had irregular palpitation and gasping for breath. After an hour or more, he went by street car to a physician; later he walked up one flight of stairs to his home where he remained abed for one day, and then up and about for one week. At one time, he suddenly fainted.

The pain subsequently moderated; at times, however, it was sharp and severe in the sternal and xyphoid regions even after slight exertion, compelling the patient to rest. He had dyspnea on exertion and palpitation even at rest. Often during the night, dosing off, he suddenly had to rise and even jump off the bed in order to be enabled to breathe. After 10 or 15 minutes, he could lie down again supported on pillows.

Examination revealed the heart apex to be in the fourth space, and the left border four inches from the midsternal line, just inside the nipple. The apex beat was felt slightly. The right border was three inches to the right of the midsternal line. There was a loud overacting first sound with a hollow tone, and ringing accentuation of the aortic second sound. The rate varied between 96 and 120 on different examinations. There were tender spots on the chest wall on the first rib, three inches to the right of the midline, and in the epigastrium, just below the tip of the xyphoid. The blood pressure was 156/98; 144/98; 142/102; 160/110 at various times, with slight pulsus alternans.

The electrocardiogram showed the T wave partially inverted in lead III, and the QRS wave notched in all three leads. The vital capacity was markedly diminished, being about 50% below the normal.

Summary—The sequence of events is so definite in this case that one cannot but relate the condition of the heart to the injury that the patient suffered. This case presents characteristically the severe sequel that may occur after extreme physical exertion. It is probable that the same work that resulted in the patient's disability could have been accomplished without

heart strain if it were not for the unusual posture he was in while at work and the poor leverage he could employ in that posture.

It cannot be doubted that a sudden organic change, possibly rupture of fibers at the base of the aorta, or even in the apex of the left ventricle took place. The classical findings of myocardial damage were present ever since the accident, including cardiac pain, tachycardia, extreme weakness, diminished vital capacity, attacks of cardiac asthma, and electrocardiographic changes.

In testing the vital capacity, the patient suffered sudden severe pain in the left scapular region with forced expiration. With repeated attempts at deep inspiration and expiration, there was a progressive diminution in the vital capacity, indicating the exhaustability of his cardiac muscle after moderate strain.

Case II.—Edward A. was a small wiry man and hard worker as a plumber's helper despite his age of 64. While lifting an icebox, he felt a sudden sharp knife-like pain in the left lower chest, shooting inward below the nipple. He remained in bed after that, unable to move because of the continuous sticking pain in his side. Since then he has had increasing dyspnea and palpitation, worse on exertion. For several nights he had to sit up because of difficulty in breathing. Such attacks have recurred almost daily and sometimes twice daily. At times he felt dizzy and had a tired, weak feeling in the chest. The precordial pain later subsided.

The heart was considerably enlarged. The apex beat was felt in the fifth and sixth interspaces, and the left border was 12 cm. to the left of the median line. The rate, seated was 80, and standing 90, with moderate sinus arrhythmia. The first sound was fair. A systolic blowing murmur was heard over the entire precordium, transmitted up to the vessels of the neck. The aorta did not percuss dilated. Occasional ventricular extrasystoles occurred, sometimes with alternate beats. These increased on exertion or coughing. There was slight tortuosity of the brachial arteries and more of the temporals. The blood pressure was 104/88.

The electrocardiogram showed marked preponderance of the left ventricle. The QRS wave was greatly widened, notched and thickened.

Summary—The patient suffered from aortic atheroma and sclerosis of the peripheral vessels. There were also chronic changes in the muscle of the heart, probably consequent on these arterial changes. The functional capacity of the heart was much impaired. The stress of lifting superinduced primary heart strain in a previously diseased myocardium.

Case III.—The history of Antonio C., 42 years old, is vivid and significant. For years he was a laborer doing strenuous work. One day, while exerting the utmost effort to lift a heavy stone onto a wheelbarrow, he suddenly felt as if something were tearing in the lower midsternal region. The pain was sharp and knife-like in character, situated below the costal margin in the left axillary line, and in the lumbar spine, and radiated up to both temples. It lasted three to five minutes while the patient remained immobile at his wheelbarrow. He became dizzy; there was darkness before the eyes, a cold sweat on the forehead, weakness and faintness. After 5-10 minutes he made an attempt to move the wheelbarrow, but found himself unable to do so. He then did lighter work for half an hour, ramming the hearth down gently on the repaired culvert.

The patient walked home about a mile, standing at rest every 5-6 blocks, and up one flight of stairs to his bed. The pain in the midsternal region and a peculiar drawing sensation in the temples continued unabated, and prevented sleep.

He remained in bed for four weeks. Dur-

ing this time there were periods of marked weakness and a feeling of tightness across the chest. The pain gradually lessened but did not entirely disappear. At times he almost fainted when standing at toilet or straining at stool. After a month he was able to walk about slowly with pain in the lower sternal region which often increased and forced him to stop to rest. On moderate exertion, he had dyspnea and palpitation, and pain in the temples. He could not sleep on his left side on account of pain.

During the two years that followed the injury, he did light work at times. Once after two hours of work, the pain increased, he became pale and had a cold sweat, and had to be taken to a hospital.

Physical examination at that time showed the left border of the heart at the nipple line 11 cm. from the midsternal line, and the right border 3 cm. from the midsternal line. The pulmonic second sound was distinctly louder than the aortic. The pulse rate was 90 lying down; 96 seated; and 100 standing. The blood pressure was 144/84.

Teleroentgenographic shadow showed the heart to be relatively normal in size and shape, the left border reaching almost an inch inside the left nipple or midclavicular line. The descending portion of the arch was somewhat prominent. The ascending portion of the aorta appeared moderately wide.

The vital capacity was moderately less than normal.

Hopping fifty times on one foot (1080 foot pounds of work) induced a heart rate of 140. After two minutes, the rate was still high, 110 per minute. The heart action after exercise was forceful with a systolic shock.

The electrocardiogram showed left ventricular preponderance. The R wave was notched in its initial phase in lead II, and in its terminal phase in lead III, making the QRS interval wider than normal. The T wave was isoelectric in lead III.

Summary—The history in this case speaks for itself. Something happened as a result of excessive physical effort from which complete recovery had not taken place after two years. The patient still suffered from pain especially after exertion. With greater effort, pallor, cold sweat, and increase of pain compelled the patient to rest.

Although the heart was not enlarged, the electrocardiogram suggested the possibility of subendothelial damage in its wall. The aorta showed slight widening. The blood pressure was normal. The rate was increased, except after long repose. Exercise induced a hyperactive heart beat.

It is difficult to define precisely the lesion in this case. Strain increased the pressure in the aorta and if it was extreme, it may have caused a tearing of the elastic and connective tissue fibers in the wall of the aorta.

Case IV.—Sebastiano P. 45 years old, worked as a laborer without difficulty until one day, when attempting to lift a heavy stone, he felt pain in the left chest which compelled him to sit down to rest. He also developed a traumatic hernia in the left groin for which he was operated on a month later under general anesthesia. Following the injury, he had shortness of breath even at rest, palpitation, and occasional sticking pain in the lower precordial region after exertion.

Three months later, his heart showed a well developed chronic mitral stenosis. There was a sharp systolic shock at the apex. In the left lateral posture there was also a presystolic thrill and rumble. The blood pressure was 152/100.

It is significant that the electrocardiogram did not show the usual graphic result of long-standing mitral stenosis. The P wave was small, indicating the absence of hypertrophy, and the other waves did not show any particular abnormality. There was left ventricular preponderance with a marked effect of respiration on the R wave in lead III. The heart rate was 120, the effect of his cardiac deficiency.

Summary—The case presents considerable difficulty because of the presence of a number of associated factors. There are first, the hard work the patient was doing before the injury; second, the development of a traumatic hernia which indicates severe physical strain; third, the presence of a chronic valvular heart lesion; fourth, the uncertain effect of the anesthesia during the herniotomy; and fifth, the rapid progress of the condition after that, totally incapacitating the patient.

The definite findings from which the rest of the case must be constructed consist of a well-developed mitral valvular lesion with myocardial weakness which has lasted an uncertain period of time. Judging from the lack of evidence at the time of operation that the patient's heart was affected, we must assume that before the alleged accident the patient's heart was in normal condition, or at least in condition adequate for the conduction of his duties and occupational labors.

This implies the development of the heart condition from and after the time of the accident. The history asserts the occurrence of pain in the left chest following the accident. How much of an effect upon the heart was produced by lifting of the stone is problematic and cannot be determined exactly. But that there was some effect must be judged from the sequence of events.

Upon the preliminary strain of the heart was superimposed the strain and toxic influence of general anesthesia one month later. Then the cardiac symptoms increased so that after three months, there was beginning cardiac failure with marked shortness of breath, palpitation, distress on even moderate exertion, flushing of the cheeks and lips with slight cyanosis, and evidence of pulmonary engorgement.

With the usual mitral stenosis of long-standing, there is commonly a history of rheumatic fever or other infection. The condition usually progresses slowly and heart failure does not take place in such a short time as in this case without evidence of acute involvement. In this case we have no adequate history, except that associated with the accident, to account for the organic condition present.

Usually also, in chronic rheumatic mitral stenosis, the electrocardiogram indicates a hypertrophy of the auricles by quite characteristic changes in the *P* wave. Here, again this is absent indicating a rapid change in the mitral valve and auricles.

In a critical analysis of this case, we are therefore compelled to assume a causal relationship between the alleged accident and the eventual cardiac failure. The intervening anesthesia no doubt contributed to the damage and must be considered as part of the alleged accident.

Case V.—Mountainy M., 25 years old, was a helper on an express wagon. While swinging a bale of paper weighing 180 lb., he was compelled to support it in a strained posture while pushing it high up on the end of the wagon. He had a feeling of numbness in the left upper abdomen. After working a little, he felt extremely faint; this recurred a few times during the succeeding days. He traveled home feeling faint and dazed, with numbness in the left side. As he walked up four flights of stairs, he had a feeling of soreness across the upper abdomen and extreme weakness.

Since then, he has had occasional peculiar

irregular heart beats. Nine days after the accident, he attempted to work at his previous occupation but could not lift anything heavy on account of immediate faintness. In one of these attacks, he actually fainted with sticking and pressing pain just below the left breast, and vomiting. After moderate exertion, he was fatigued and had dyspnea and palpitation.

The heart was not enlarged; the sounds were good. There were tender spots on the fifth and sixth ribs three inches to the left of the midline. The blood pressure was 140/70. The electrocardiogram was negative.

SUMMARY

Immediately after exertion, the patient felt a peculiar sensation in the left side of the upper abdomen, and enough discomfort to desist from further work. He then experienced faintness, weakness and other sensations attributable to the circulatory system. Later, after moderate effort, he had slight dyspnea, palpitation, and a feeling of fatigue.

Although there were no other physical signs of cardiac involvement, there were tender spots on the chest wall located over the fifth and sixth left ribs. Otherwise, the main reliance must be placed upon the slight symptoms present.

The casual relationship of the particular over-stress recorded to the heart-strain that ensued is evident.

Case VI—Fred R., a mechanic 37 years old, was pulling a heavy wind organ, when he was suddenly seized by a severe sharp, momentary pain localized below the left nipple, and a sense of suffocation. He rested seated for about two hours, with a feeling of extreme weakness and tenderness below the left breast. The next day, he undertook only supervising and stopped work after several hours.

Since then, he had dyspnea and palpitation, and a dull precordial pain after exertion such as climbing steps or crossing a street rapidly; and he often felt irregular heart beats.

Physical examination five months later showed the heart enlarged to the left and rather rapid, 90 beats per minute. The apex beat was just beyond the nipple line in the fifth space, in which region there was a tender spot on the sixth rib. The blood pressure was 122/82.

From the available tables the patient's vital capacity was 25% below the normal. The electrocardiogram gave no data of interest besides a tendency to preponderance of the left ventricle. Teleroentgenographic shadow showed slight enlargement of the heart both to the left and right, but the aorta was of normal width. There were signs of mild hyperthyroidism with slight digital tremor. A year later the basal metabolic rate was +20.

SUMMARY

The patient was suddenly seized by a sharp pain in the region of the heart apex with a feeling of suffocation and extreme weakness. Subsequently he had a tender spot on the precordium and pain, dyspnea, and irregular heart action after exertion. A myocardial change was produced by strain, and in the process of healing there was hypertrophy of the left ventricle.

Case VII—Hyman K., aged 21, a shipping clerk of small build, while moving a case weighing 700-800 lbs., felt a sticking pain shooting across the precordial region to the right of the sternum. This recurred whenever he lifted something heavy. He also developed moderate dyspnea and palpitation on exertion.

The heart was found slightly enlarged. Its left border percussed just outside the nipple line. There were tender spots over the fourth and fifth left ribs and over the left border of the heart. The blood pressure was 146/100. X-ray showed the heart slightly prominent to the right. The electrocardiogram was negative.

SUMMARY

Immediately following lifting, the patient had a sticking pain in the pre-

cordium. This recurred in a lesser degree when the strain was repeated, and indicated some effect, organic in nature, upon the heart and aorta. The casual relation of the effort to the cardiac pain is obvious in this case.

Case VIII—Emil O. was a robust iron worker 59 years old. While lifting the end of an iron railing weighing 1500 lbs., he suddenly felt a severe, sharp, burning pain radiating from the right upper abdominal region, obliquely to the precordial and left pectoral regions. He screamed with pain and distress, unable to catch his breath, with darkness before his eyes. He was assisted by two men to a hospital where he remained under observation for two weeks. The pain across the front of the chest persisted, somewhat moderated, but increased with exertion.

The heart was found slightly enlarged to the left, its border being beyond the nipple line. The apex beat was barely palpable, and the sounds were of poor muscular quality. There was a tender spot on the third and fourth ribs, 2 inches to the left of the midsternal line.

The blood pressure, on different occasions, was 200/112; 236/110; 220/118, with distinct pulsus alternans. The liver was considerably enlarged below the free border and there was moderate pretibial edema. The vital capacity was greatly reduced. The electrocardiogram showed right bundle branch block.

Summary

Suddenly, following great strain in lifting, the patient had the typical pain and other symptoms which indicate strain of the heart muscle. We must assume from the labor in which the patient was engaged, that his heart condition was at least able to endure the strain of his occupation. Without doubt, certain arterial changes that come with age had already initiated changes in the myocardium, but these were not sufficient to disable the patient in any way. It can definitely be asserted that the heart strain in this case resulted directly from the injury, as an aggravation of his previous condition.

Case IX—Charles W. is an electrician 26 years old. While lifting a transformer weighing 150 lbs., he felt a sudden sharp knife-like pain along the nipple line from the left shoulder down to the lower left costal margin, with a sudden, quick and irregular beating of the heart, both of which lasted about two minutes. He remained standing for a few minutes, immobilized by the pain, but continued to work more moderately, feeling fatigued.

The pain returned that night after supper, as a steady pressing sensation just below the left nipple region; it lasted all night and was associated with some palpitation. In the morning, the pain was greatly relieved, but it recurred two days later as a dull pain over the lower precordium. The patient remained at home and abed for two weeks, and then returned to lighter work.

Since then he has dyspnea, rapid heart action and palpitation on ascending hilly ground, or after moderate exertion such as his present work requires—which consists of climbing poles. Recently, dizziness and scotomata appear after exertion, but never faintness. The pain has recurred three or four times and is relieved by resting for about an hour.

The heart was not enlarged, and presented a normal systolic impulse. There were frequent ventricular premature beats, most of these not transmitted to the radial pulse. The aortic second sound was less marked than normal. The rate seated was 72, including extrasystoles; standing, it was 80. The blood pressure was 126/86. The extrasystoles showed very low pressure. The vital capacity was 11% below the normal.

The electrocardiogram showed frequent ventricular premature beats arising from the base of the right ventricle. The premature beats occurred early, producing no effect on the radial pulse.

Summary

The sequence of events is so definite in this case that one cannot but relate the condition of his heart to the injury that the patient suffered. Some definite organic change resulted from the excessive sudden strain which he endured at the time of his accident. It is not usual for a heart which has suffered from a strain of this character to undergo absolute restoration to normal.

Case X—Joseph D. was a laborer 36 years old. While helping support the end of a heavy iron pipe on his left shoulder, he felt a slight pain or soreness in the left chest, from the shoulder down to below the breast. This became worse when he was relieved of the weight, with a feeling of faintness. The pain persisted; the patient did lighter work for the day, but remained at home subsequently, complaining of dyspnea and palpitation on exertion, and of continuous aching pressing pain in the precordial region. He could not sleep on the left side with comfort.

On examination, the heart was not enlarged. Over the apex, the first sound had a peculiar hollow quality. There was a slightly tender spot over the fourth rib, four inches to the left of the median line.

The vital capacity was very much reduced. The blood pressure was elevated—142/104; 158/114. X-ray showed slight dilatation of the ascending arch of the aorta. The electrocardiogram showed left ventricular preponderance. The T wave was inverted in lead III and the P wave was notched in lead II.

Summary

During strenuous effort, the patient felt pain and soreness in the left chest. This persisted and was subsequently associated with dyspnea and palpitation. The symptoms developed before the presence of obvious physical signs. When the symptoms are consistent, as in this case, and the physical signs are suggestive and not contradictory, the patient must be given the benefit of the doubt as to his disability from strain of the heart.

Case XI—John B., a robust and rather plethoric man of 60, was trapped in a small room by a fire in the exit. He became greatly excited, and endeavored to pull apart the iron bars across the windows in the room. In doing so, he struggled frantically. He remembers being dragged away from the window in a semi-conscious condition, quite exhausted from his attempts to escape. He was extremely dyspneic and had a sticking pain in the left sternal and precordial regions, or a sensation of heaviness in the lower sternal region.

Following the accident, he remained in bed for eight days with weakness, dyspnea and cough. Since the accident, he had dyspnea on moderate exertion with palpitation after walking 5-6 blocks. Orthopnea was present.

The heart was slightly enlarged to the left, its left border being outside the nipple line. Aortic dullness was 1¾ inches to right of the midsternal line. The sounds showed deficient muscular quality. The blood pressure was 192/100, and the vital capacity was 36% below the normal.

The electrocardiogram showed left ventricular preponderance. The QRS wave was widened to 0.12 seconds.

Summary

In the distress and alarm which occurred during an accident, the patient exerted extreme physical effort in an attempt to save his life. During this, he suffered symptoms referable to his heart as well as to the skeletal muscles (Left inguinal traumatic hernia).

A moderately advanced myocardial condition with high blood pressure apparently existed before the accident. It is however doubtless that there occurred an aggravation of the condition. This takes a long time to ameliorate. The patient's dyspnea was improved considerably several months

after the accident and he could undertake moderate physical activity.

Case XII—George K., a cook and counter-man, 30 years old, had worked at his occupation for several years without discomfort. One day, while carrying a bag of sugar weighing 100 lbs. up one flight, he felt a tearing pain below the left breast, radiating to the region of the navel. With this, there were weakness, marked pallor, cold sweat and vomiting. He remained seated for two hours without relief. For the next three weeks, he was in bed with dyspnea, palpitation, and continued pain. After returning to work for several hours, the symptoms recurred. Subsequently he also had occasional attacks of extremely rapid heart beating of sudden onset, lasting a varying period of time.

The heart showed a heaving apex impulse far to the left and below its normal position. The enlargement was also evident to the right. Over the apex there was a faint systolic thrill and murmur transmitted upward to the aortic area. There was a marked loud, prolonged, blowing diastolic murmur over the aortic area replacing the second sound and transmitted down along the sternum. A presystolic "Flint" murmur was also audible. There was unusually marked tortuosity of the temporal and brachial arteries, and a Corrigan and capillary pulse. The blood pressure was 134/62, and the vital capacity was considerably below normal. The Wassermann test was positive.

X-Ray showed the heart enlarged in all its diameters, with accentuation of the right auricular and left ventricular curves.

The electrocardiogram showed left ventricular preponderance and numerous premature beats arising from two separate foci—one in the left base and the other at the right apex.

Summary—For three and a half years the patient pursued the same occupation without any difficulty or complaint. At the time of the alleged accident, there suddenly developed symptoms indicating a sudden tearing lesion within the chest. The symptoms were severe and have practically disabled the patient permanently. Each attempt at work is followed by distress with the need of hospital care, and attacks of paroxysmal tachycardia often occur.

It is evident, however, from the physical examination that there was a premature development of advanced arteriosclerosis involving the peripheral arteries and arterioles. There was an excessive degree of vascular change rarely seen at the patient's age.

The physical signs showed a marked aortic diastolic murmur which could be produced by rupture of the aortic valve. The valve was doubtless diseased prior to this, but muscular strain may have caused the sudden development of aortic regurgitation.

The causal relationship between the accident and the development of the aortic regurgitation is direct in this case. Accepting a pre-existing arteriosclerosis, rupture of an aortic valve in consequence of sudden muscular strain is an accident which is not very uncommon. It does not usually occur in a previously normal valve, but in one damaged by a pre-existing atheroma and fibrosis due to arteriosclerosis, syphilis, or other degenerative disease. The Wassermann test in this case indicated a possible luetic cause for the entire condition.

Case XIII—Frederick F., aged 47, did very hard labor driving a truck and lifting cases of 500-900 lb. each. One morning after working he became dizzy and felt weak, and on his return to the place of business he could hardly stand up. There was no chest or abdominal pain. The patient returned to work after two days and continued at work for four months.

Since the onset, however, he felt fatigue and dyspnea after exertion, but no pain. Three months after the accident, he developed swelling of the feet and legs, marked

orthopnea and a distressing cough which was worse on lying down.

The heart was enlarged to the left, the apex being in the fifth space outside the nipple line. The right border was 5 cm. from the midsternal line. The aorta was widened. There was an audible third heart sound due to auricular systole. The rate was 114, with frequent ventricular extrasystoles. The blood pressure was 160/120 with marked pulsus alternans. The axillary, inguinal and epitrochlear glands were enlarged. The vital capacity was 60% below normal. A blood Wassermann test gave a ++++ reaction.

The electrocardiogram showed left ventricular preponderance, low voltage, and an occasional ventricular extrasystole arising from the right base.

Summary—The patient suffered from chronic myocarditis with high blood pressure and marked pulsus alternans. Physical examination indicated a failing heart with congestion at the bases of the lungs and marked edema of the legs. The pathological condition in the heart was syphilitic and did not depend in this case upon, or have any relation to his work.

Case XIV—Frank S., aged 40, was a laborer. While hoisting a large tube of concrete weighing between 300 and 500 lb. by hand, he felt a severe aching pain in the lumbo-sacral region and spine which prevented him from continuing his work. After coming home, he felt a smothering sensation with very rapid palpitation and a feeling of heaviness across the lower sternum. He was in fear of dying. These symptoms gradually subsided after four days.

He then had palpitation after walking a short distance or upstairs, occasional dyspnea and weakness during the night, with a feeling of smothering.

The heart was not enlarged. The first sound was deficient in muscular quality; at the apex there was a soft short blowing systolic murmur not transmitted. The heart rate was 60 per minute, and the blood pressure was 122/68. The vital capacity was below normal. The electrocardiogram was negative. X-ray showed a "drop heart."

Summary—The symptoms of dyspnea and palpitation may be due to the patient's heart condition. The pain the patient experienced in the lumbosacral region was interpreted on the basis of a spinal arthritis. The other cardiac symptoms were the result of heart strain due to the recorded accident.

Case XV—John G., a man of 32, was a helper on a truck. His work consisted of carrying loads of brick of 50 lb. or more. For six months prior to his present illness he had dyspnea and palpitation on exertion. In the course of his work he felt momentary darkness before the eyes and faintness and headache. One day he began to feel a slight sticking pain in the region of the left breast. Since then he had occasional localized sticking pain in the left chest.

His heart showed a rough blowing systolic murmur over the apex and aortic area. The peripheral vessels were slightly tortuous. The Wassermann test was negative. The blood pressure was 144/88. The electrocardiogram was negative.

Summary—A patient with cardiovascular disease would naturally feel symptoms of distress if he undertook a strenuous occupation. The patient had symptoms of cardiac distress for six months prior to his complaint which his work naturally aggravated.

It is probable that in consequence of the repeated liftings and pullings there was a cumulative effect upon the heart and aorta. The aortic condition was of long standing, which the work temporarily aggravated.

There cannot be assumed any causal relationship between his work and the cardiac condition that the patient suffered previously. The occupational stress may have aggravated his myocardial deficiency. But from a compensation standpoint there was no accident as a factor in the production of heart strain.

Polycystic Disease of the Kidneys

By George Morris Piersol, M.D., *Philadelphia, Pennsylvania.*

Although polycystic degeneration of the kidneys cannot be looked upon a rare disease, it may be regarded as relatively uncommon. Therefore, it seems justifiable to add to the group of reported cases.

The frequency with which polycystic disease occurs may be judged from the following statistics. In 1887 Neumann (1) reported fourteen bilateral and two unilateral cases in 10,177 necropsies. Preitz in 1905 working up the Kiel Institute material found sixteen cases in 10,000 autopsies. Bugbee and Wolstein (2) in 4903 autopsies on children, recorded twenty cases. In 1927 Gruber at Jena collected eight bilateral cases in 3,500 postmortem examinations. During the past three years only five instances of the condition have been found in the necropsy material at the Philadelphia General Hospital. At the Boston City Hospital, Garceau met with ten cases in 2,439 necropsies. A few years ago Barnett was able to collect a total of 251 cases. Since then 238 additional cases have been recorded. An idea of the frequency with which polycystic disease of the kidney is met with in our large general city hospitals may be gained from a statement made by Atonna and Morrisey (3), that during the four years from 1922 to 1926 inclusive, the total number of cases reported from the hospitals of New York City averaged only eight per year.

Two striking examples of this disease recently encountered awakened our interest in this condition.

The first case was that of an Irish laborer, aged 42 years, admitted during the winter of 1927 to the writer's service at the Philadelphia General Hospital. His outstanding symptoms were swelling of the abdomen, pain in the left upper abdominal quadrant, swelling of the legs, cough and dyspnoea.

The patient stated that he had always been unusually well until August, 1926, when he developed acute abdominal pain, was taken to a hospital in Philadelphia where his appendix was removed. From that time on he had been sick, complaining of the above noted symptoms. His strength failed so that for the four months prior to admission, he was unable to work. He had also developed since his operation, a decided nocturia.

Aside from the fact that he had been for years a heavy drinker, there was nothing significant in his previous medical or social history. His family history was also unimportant. There was nothing to suggest the existence of polycystic kidneys in any of his forebears.

It is interesting to note that a report on his operation in August, 1926, from the hospital where it was performed, states that a somewhat inflamed appendix was removed, that his liver was enlarged, contained multiple cysts, the lower border being four to five inches below the costal margin. The appendix was removed, and an hepatic cyst was punctured and drained. The patient made a fair recovery and was discharged

with a diagnosis of Hepatic Cyst; Impending Cirrhosis of the Liver.

The salient features of our physical examination of this patient were as follows:—

The patient was a well developed, but rather poorly nourished white male. There was a left peripheral facial palsy due to a severe head injury in 1920. The lungs were normal except for some crackling râles at the right base. There was a distinct widening of the costal angle due to the marked outward flare of the lower ribs as from pressure. The apex beat was visible and palpable in the fifth interspace on the left mid-axillary line. Percussion showed decided left sided cardiac enlargement. The aortic second sound was louder than the pulmonic. At the apex a soft, non-transmitted systolic murmur was heard.

Chief interest centered in the abdomen. There was distinct bulging of the left side of the abdomen and of the left flank. A marked ventral hernia was present. The liver was enlarged, hard, non-tender and was palpable two inches below the costal border. The left side of the abdomen was filled with a large, hard, irregular, tender mass. This mass extended down to the left iliac crest and toward the mid-line to within two inches of the umbilicus. It moved with respiration, was definitely palpable bi-annually and caused marked fulness in the left flank.

A summary of the laboratory examinations is viz:—Urine: acid, clear, Sp. Gr. 1006-1010. All specimens contained definite traces of albumin. Glucose was always negative. Microscopically no casts were found, but leucocytes and a few red blood cells were always present.

On admission his hemoglobin was 55%; RBC. 2,950,000; leucocytes 7,200. Polymorphonuclears 76%, Lymphocytes 24%. In several subsequent differential counts the eosinophiles were increasd, ranging from 2 to 5 per cent.

His blood Wassermann was negative to all antigens. His blood sugar was 155 mgms. per 100 c. c. of blood. The urea nitrogen was 40 mgms. per 100 c. c. of blood. On the day of admission his temperature was normal, his pulse slightly increased and his systolic blood pressure 130; diastolic 60.

A tentative diagnosis of Cirrhosis of the Liver, or Banti's Disease was made.

Three days after admission the patient had a generalized convulsion epileptiform in character. After this he became toxic, semi-stuporous and vomited repeatedly. There was no hematemesis. He became obstinately constipated. His toxemia improved, but the vomiting, especially after taking food, continued. Pain in the left side of the abdomen increased and the mass became larger and felt more nodular.

With the thought of gastro-intestinal malignancy in mind, a fractional gastric analysis was done. This showed a total absence of free hydrochloric acid, but no blood. A fluoroscopic examination of the gastro-intestinal tract showed *no* organic lesion of the stomach, which was displaced to the right, but a herring bone appearance of the jejunum thought to be due to either pressure of adjacent organs or an obstructive lesion at the jejuno-ileal junction.

In as much as the vomiting continued and the patient's condition was growing steadily weaker, a surgical consultation was held and surgical intervention advised.

An exploratory laparotomy was done under nitrous oxide anesthesia. The liver, spleen and gall bladder were found normal. The abdomen was found almost filled by two large retro-peritoneal polycystic masses. In spite of nine months of varied observation the correct diagnosis of congenital, bilateral, polycystic kidneys was then made for the first time.

Within twenty-four hours after operation the patient died of bronchopneumonia with pulmonary edema. An autopsy was performed. The essential findings at autopsy were as follows:—

The heart was moderately enlarged due to left ventricular hypertrophy. The mitral valve was normal. The coronary arteries showed a slight degree of atherosclerosis. The aorta showed a moderate degree of arteriosclerosis. Both lungs were the seat of old pleural adhesions and of recent congestion, edema and bronchopneumonia. When the abdomen was opened, a striking picture was presented. Both kidneys were seen to be markedly enlarged and cystic. They occupied most of the abdomi-

nal cavity. Each kidney extended from the pelvic brim to the dome of the diaphragm. This is well shown in the photograph taken with the kidneys in position. (Fig. 1.) The left kidney weighed 1450 gms., and measured 33x18x13 cm. The enormously enlarged kidney was made up being largely replaced or compressed by the multiple cysts.

The spleen was somewhat enlarged, soft, and congested. The adrenals were plastered on to the upper poles of the kidneys and appeared quite normal. The liver was about normal in size, weighing 2050 gms.

FIG. 1.—Enormous bilateral polycystic kidneys filling almost the entire abdominal cavity.

of innumerable cysts of varying size. The largest cyst measured 5x6 cm. in diameter. The right kidney weighed 2070 gms.; was fully as large as its fellow and was identical in structure, being largely converted into a mass of various sized cysts. Upon section little normal renal structure remained in either kidney, the normal parenchyma Its capsule was smooth, the lower margin fairly sharp. On section two small cysts were revealed each about 1.5 cm. in diameter, with thin walls and containing clear fluid. The remainder of the gastro-intestinal tract was negative.

The final anatomical diagnosis was,

Congenital Polycystic Kidneys; Cysts of the Liver; Moderate Arteriosclerosis and an Hypertrophied Heart.

The autopsy clearly proved that the masses which had been palpated during life, and were regarded as an enlarged liver and spleen, were actually the two large polycystic kidneys. The liver and spleen were never palpable.

In this case a correct clinical diagnosis was never made until after exploratory operation. We failed to interpret correctly the abdominal signs. We overlooked the possible significance of the hypertrophied left ventricle, the accentuated aortic second sound, and the evidence of arteriosclerosis. Our minds were so fixed on other diagnoses, that no one gave proper weight to the persistent albuminuria, the occasional red cells in the urine, or the definitely increased blood urea nitrogen. If these findings that pointed to kidney involvement had been given due consideration, the existence of renal tumors might have been suspected and proved by pyelography and functional kidney tests.

The second case occurred upon the service of my associate, Dr. H. L. Bockus, at the Hospital of the Graduate School of Medicine of the University of Pennsylvania. I am indebted to Dr. Bockus for the opportunity to study and report this case.

The patient was a business man, aged 64 years, who was admitted on 11-14-1926 as a suspected case of pernicious anemia or carcinoma of the intestinal tract. His chief complaints were weakness, nausea, vomiting, loss of weight and anemia. For eighteen months he had had gastro-intestinal symptoms, with the exception of one attack of alleged renal colic in August, 1925. This cleared up and he had no further renal symptoms. Three months before admission his nausea and vomiting became persistent. He lost weight and complained of numbness and tingling in the extremities.

On admission the outstanding features of his physical examination were marked pallor, a definite mouth infection, infected tonsils, a chronic glossitis, marked left ventricular hypertrophy, an accentuated aortic second sound, palpable vessels and decreased knee jerks. The abdomen was soft and relaxed. The liver and spleen were not palpable. On the right side of the abdomen along the line of the ascending colon and clearly not connected with the liver, was a mass the size of a small apple lying rather superficially and easily palpable. At the time this was looked upon as a carcinoma of the colon.

The laboratory findings soon put a different aspect on this case. On admission his systolic blood pressure was 218, diastolic 165. The urine had a specific gravity varying from 1008-1010, contained a heavy cloud of albumin, but no glucose and no casts or red blood cells. The hemoglobin was 32, erythrocytes 1,900,000 and leucocytes 5,300, with a color index of 0.8; polymorphonuclears 87%, lymphocytes 11%, transitionals 2%. There were no nucleated red cells nor any blood findings suggestive of true Addisonian anemia. The blood Wassermann was negative to all antigens. The first blood chemistry showed the blood sugar to be 87 mgms. per 100 c. c.; uric acid 3.5 mgms.; creatinin 14 mgms.; urea nitrogen 160 mgms.; cholesterol 130 mgms., and chlorides 496 mgms. A subcutaneous phenolsulphonphthalein test showed no dye eliminated. Later when the dye was injected intravenously, 12½% per cent was recovered at the end of the first hour, and a like amount at the end of the second hour. A fractional gastric analysis showed normal gastric function, free hydrochloric acid being present in considerable quantity. An x-ray study showed a dilated aorta, a normal stomach and small intestines and a colon pushed down by a mass that was obviously not related to the bowel.

The blood findings and gastro-intestinal studies clearly eliminated the possibilities of pernicious anemia or intestinal malignancy.

All the clinical and laboratory findings pointed clearly to renal insufficiency in a chronic nephritic with hypertension.

Further progress of the case bore this out. The patient became progressively more anemic and weaker. Five days after admission he was stuporous, had a uremic odor to his breath, and his blood urea nitrogen was up to 164 mgms. per 100 c. c.; creatinin 30.4 mgms. and the CO_2 of the plasma equalled 27 vol. %. A transfusion was done with little success at this time. He continued to become more toxic and died in uremia three weeks after admission. Three days before death his creatinin was 21.2 mgms. and his urea nitrogen was up to 170 mgms. per 100 c. c. of blood.

During the entire course of his illness the mass in the right upper abdomen was constantly palpable and a less distinct mass could at times be felt in the left side. A week before death he was seen by Dr. J. B. Carnett in consultation, who suggested the diagnosis of bilateral polycystic disease of the kidneys because of the somewhat cystic feel of the right-sided mass, the exclusion of all other explanations for the abdominal mass, and the co-existence of hypertension and renal insufficiency.

The significant features of the autopsy in this case were:—Healed tuberculous lesions with adherent pleura at the apices of the lungs with terminal congestion and edema. There was slight cardiac hypertrophy with chronic fibrous interstitial tissue increase. The gastro-intestinal tract was negative. The liver was not enlarged, but contained a few small cysts. The spleen was not enlarged but was the seat of chronic fibrosis. The masses felt were a pair of definitely enlarged, congenital polycystic kidneys. The right kidney weighed 1095 gms., the left kidney 890 gms. Both kidneys contained innumerable cysts of varied size. These cysts were lined with low cuboidal and even flattened epithelium. The tissue between the cysts contained Malpighian bodies and tubules and was the seat of chronic interstitial nephritis.

The fluid from the cysts examined postmortem, was slightly turbid and contained *non*-coagulable nitrogen fractions in the following amounts. Uric acid, 20 mgms. per 100 c. c.; urea nitrogen 300 mgms. per 100 c. c. and creatinin 58 mgms. per 100 c. c.

In this second case the evidence of renal involvement was much more definite than in the first, but the abdominal tumors were much less obtrusive. As in the first patient, the original diagnosis was wrong and it remained for a surgeon to make a correct one.

Polycystic degeneration of the kidneys may be roughly divided into four groups.

1st. Those in which the condition develops at or shortly after birth. These children die promptly after birth. In this group the condition is usually associated with other developmental defects as cleft palate, imperforate anus, cysts of the ovary, supernumerary digits, etc. In the other groups the condition does not manifest itself until adult life.

2nd. The second group presents nothing that suggests the existence of polycystic kidneys. In this type renal insufficiency develops unexpectedly and is promptly fatal. The true nature of the renal lesion is only discovered at autopsy.

3rd. Group three shows the usual manifestations of chronic hypertensive nephritis often associated with progressive weakness and a marked secondary anemia. The polycystic renal degeneration is only recognized when the kid-

neys become expanded and are definitely palpable cystic tumors. Most of the cases recognized clinically have been in this group. The second case here reported clearly belongs in this class.

4th. The fourth group comprises those cases in which the first symptoms point clearly to urinary tract disease such as a definite renal tumor, hematuria, renal colic, persistent fullness, pain and dragging in the iliocostal space. These cases are usually recognized more easily and earlier. Our first case more nearly fits into this group.

According to Cabot's series, the greatest number of cases of polycystic renal degeneration presents symptoms between the fortieth and sixtieth years. The tumors are rarely found after infancy until the eighteenth or twentieth years are passed.

The condition is said to be more common in women than in men. Heredity seems to play a definite rôle in its production. In 1902 Osler reported a family in which the disease occurred repeatedly in different members. Crawford (4) reported a case in which the disease had occurred with amazing frequency in various members of the patient's family. He quotes Borelius and Love and Richmond, as having made similar observations.

The condition is more often bilateral than unilateral. Sieber (5) found only 10 unilateral cases in 150 cases proved by autopsy. In adults the most commonly associated pathological conditions are cysts of the liver, arteriosclerosis and cardiac hypertrophy.

The diagnosis depends largely upon finding in one or both flanks, irregular, nodular tumor formations having the general outline of the kidney. When the renal tumors are bilateral the diagnosis may be made with certainty, as polycystic disease is practically the only cause for bilateral kidney tumors. These tumors may exist for years without symptoms. As a rule, however, albuminuria with other evidences of chronic renal disease develop. Hematuria irregularly intermittent is reported in fifty per cent of cases. When present it is an aid to diagnosis. Pyelography, especially advocated by Atonna and Morrisey (6) and functional kidney tests are useful procedures in arriving at a diagnosis. The former is particularly helpful in differentiating polycystic disease from hydronephrosis, pyonephrosis and hypernephroma. In many cases, especially those in which the tumor is inconspicuous, the diagnosis is difficult and frequently unsuspected.

The prognosis in polycystic disease of the kidneys is ultimately uniformly bad. The earlier the age of onset the worse the prognosis. It is rare for adults to survive more than from one to ten years after symptoms develop. The majority of adults succumb in their fourth decade.

The treatment of the condition is thoroughly unsatisfactory and is largely medical. The bilateral nature of the disease makes nephrectomy out of the question. In twenty-two cases nephrectomy was attended by a mortality of 31.89% and only two cases lived beyond two years. Rovsing (7) has advocated puncture and drainage of the cysts for the relief of pressure. His results, however, were of only temporary benefit. Renal infection,

urethral obstruction and stone may demand radical surgical interference. On the whole, it is safe to say, that the majority of cases will live as long and do as well under palliative medical management.

The pathogenesis of the polycystic kidney has always aroused considerable interest. Virchow held that the uriniferous tubules of the kidney become blocked off as the result of inflammatory tissue in the renal papillae thus causing true retention cysts. This theory has few, if any, advocates today.

Another group of pathologists contended that the cysts are new growths and that they are virtually cyst-adenomata. Subsequent observations have failed to substantiate this view.

The theory that today is most generally accepted is that the cysts are the outcome of a developmental defect. Recently Kampmeier (8) has carried on extensive embryological studies on the origin of congenital renal cysts. His conclusions in brief are as follows:—"Every human individual during fetal life normally passes through a period characterized by the presence of numerous cystic renal tubules. Such a normal physiological event, however, may be converted into an abnormal or pathological condition if such tubules do not give way at the end of their allotted time, but continue to grow and expand to the detriment of adjacent structures." He goes on to show how isolated renal cysts can easily result from the persistence and expansion of cystic tubules which fail to collapse and finally points out that congenital cystic kidneys where the entire organ is affected, may have their inception in the wide-spread persistence and cystic degeneration of the cystic uriniferous tubules which he has described.

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Chronic Articular Rheumatism of the Vertebrae Followed By a Progressive Degenerative State of the Spinal Cord*

By Alfred Gordon, M.D., F.A.C.P., *Philadelphia*

CHRONIC articular rheumatism from the anatomical standpoint is invariably of the same character irrespective of its localization, but from the clinical standpoint its manifestations are polymorphous. Particularly interesting is the affection when it is localized in the vertebrae and especially in the intervertebral spaces, because in some such cases the course of the manifestations may be so insidious that their evaluation may be overlooked for a long time until gross, serious and incurable symptoms referable to the spinal cord via the roots become conspicuous. The two cases reported below present a striking illustration of such an occurrence.

Case 1.—G. F., middle-aged man, commenced seven years ago to experience a weakness in both legs; more in the right than in the left. The condition gradually increased so that he had difficulty in walking. At no time did he suffer pain or have any subjective sensory disturbances, beside a sensation of heaviness. He came under my observation about three months ago and the following condition was revealed. In walking he frequently stumbles, especially with the right foot. Going down or up stairs or getting up a curb on the street, or walking in the dark the patient experiences considerable difficulty. The toes frequently strike the ground, although there is no marked foot-drop. However, there is some weakness in the extensor muscles of both legs. There is no atrophy of the musculature in the affected extremities. There is no ataxia in gait and station. Romberg sign is absent. Objective sensibility is intact. Resistance against examiner's hand is diminished in every segment of the limbs. The patellar tendon reflexes are greatly increased. Ankle-clonus is absent on both sides. The plantar reflex is frequently extensor by all methods on the right side, but sometimes the toes remain indifferent, but at no time do they flex. On the left side the toes invariably remain indifferent on stimulation of the plantar surface. The abdominal and cremasteric reflexes are abolished on both sides. A detailed examination of the upper limbs, of the pupillary reactions, of ocular muscles, of the fundus oculi, of the sphincters, gave negative results. Wassermann test of the blood and spinal fluid, the colloidal gold reaction, urine, the blood chemistry—have also been negative. The patient experiences great discomfort in the lumbar region in leaning forward or backwards or else in lifting heavy objects. Only occasionally has he pain in the lumbar region radiating down the legs. X-ray examination of the spine revealed a complete obliteration of the intervertebral spaces at the lower levels of the 3rd and 4th lumbar vertebrae, also thickening of the lateral surface of several vertebrae. Such a condition is due to rheumatic deposits.

To sum up, we are dealing with a case of chronic rheumatism of the spinal column

*Patients exhibited at the February Meeting of Philadelphia Neurological Society.

in which gradually and imperceptibly disturbances referable to the motor tract of the cord made their appearance without affecting the sensory tracts. The diagnosis is therefore "Subacute degeneration of the motor pathway of the spinal cord as a consequence of a rheumatic obliteration of the intervertebral spaces."

Case II.—M. L., 56 years of age, began to notice the present disorder about 10 years ago. At that time he commenced to have some discomfort in the lumbo-sacral region. Soon involuntary spasmodic contractions appeared in the right leg. They would appear in walking or standing. Weakness soon developed in both legs, more in the right than in the left. This paretic condition progressed very slowly, but the spasmodic contractions gradually decreased.

At present the resistance of the muscles in the lower extremities is very slight, as it can be easily overcome, with predominance on the right side. There is awkwardness in walking and in going up and down an elevation. Walking in the dark is hazardous, as the patient feels insecure. Lately a weakness appeared in the right arm and hand, also occasional spasmodic contractions similar to those of the lower extremities. There is no ataxia in station or gait, but there is a certain amount of dragging in the right leg. There are no objective sensory disturbances in any of the four extremities. Patient complains of heaviness in the legs and of great discomfort in the lower back. There is no atrophy of the musculature of the limbs. The patellar tendon reflexes are exaggerated on both sides, more on the right than on the left. There is a slight ankle-clonus on the right side. The plantar reflex is present in extension on right and indifferent on the left side. The abdominal reflex is diminished and the cremasteric reflex is abolished on the right side. The sphincters are intact. Examination of the eyes gave no abnormal findings. The Wassermann reaction of the blood and spinal fluid, also the colloidal

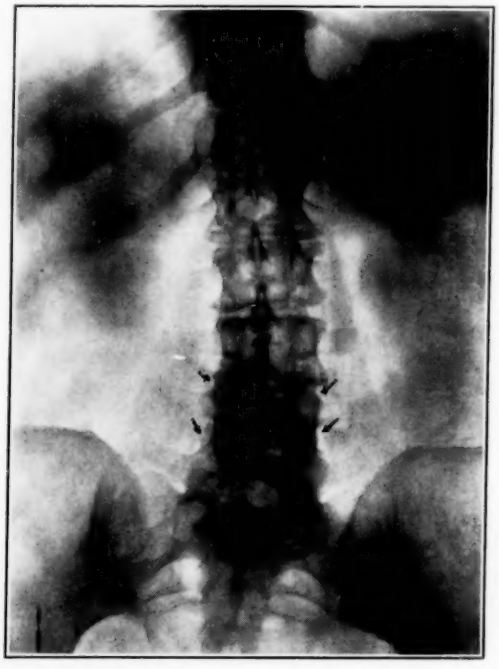

FIG. V.—Case I. X-ray picture of rheumatic changes in lumbar vertebrae.

gold reactions—are all negative on repeated tests. Urinalysis is negative. Blood count and blood chemistry are all normal. Because of the persistent discomfort in the lower back an x-ray examination of the entire spine was made and it shows a chronic osteo-arthritis of the lumbar spine, also a sacro-iliac synchondrosis.

To sum up, the second case presents a chronic rheumatic state of the lumbar spine nevertheless spasticity which is to be expected by the nature of the localization of the disorder is totally absent. On the other hand there is no genuine flaccidity, the legs move slowly and heavily and the resistance can be overcome. The two cases are not examples of a well-developed typical Spastic

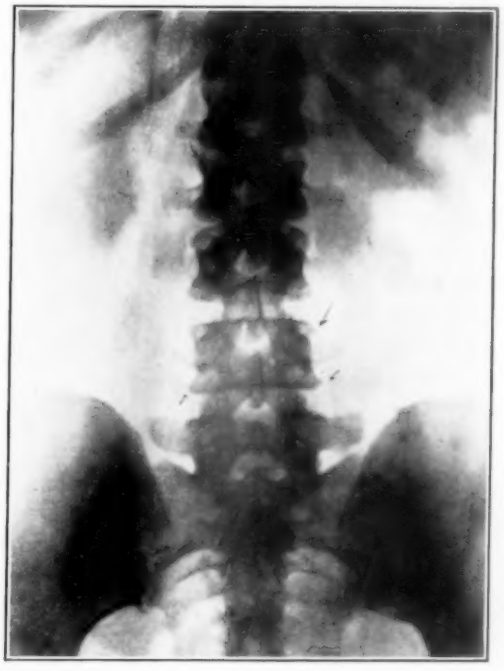

FIG. 2.—Case II. X-ray picture showing chronic osteo-arthritis of lumbar spine.

of 10 years' duration, during which period motor phenomena very insidiously developed indicating an invasion of the motor tract of the spinal cord.

The two cases herein reported are examples of exclusive motor tract involvement which chronologically followed an onset of a rheumatic condition of the vertebrae. The striking feature in them lies in the fact that while all the symptoms indicate a condition found in primary lateral sclerosis, Paraplegia which pathologically is characterized by a total degeneration of the pyramidal tracts. In our cases we have all the other evidences of an invasion of the same tract except spasticity of the limbs. Moreover, in spite of the duration of the disease (10 and 7 years respectively) it has not reached the degree of motor degeneration which is found in typical Primary Lateral Sclerosis. One is therefore led to

conclude that in both affections the seat of the morbid process is identical but the degenerative process is probably different. Spasticity is characteristic of Spastic Paraplegia, while it is absent in our two cases in spite of the fact that all other manifestations are indicative of a lesion in the same pathway.

An analogous condition we find, when we attempt to differentiate the classical system diseases of the spinal cord from the degenerative changes in the cord associated with severe anemia. In both cases there are symptoms of involvement of the posterior and lateral columns, but certain symptoms may be pronounced in one, not in the other. For example, in some cases ataxia may be accompanied by spasticity of the extremities, in other cases there may be ataxia and hypotonia of the limbs. In still other cases the disease commences with ataxia and spasticity and then later the spasticity disappears and flaccidity makes its appearance. In the affection due to anemia the onset is usually extremely slow and not infrequently spasmodic contractions of the involved muscles occur. Finally in the same disease the motor impotency never affects the upper extremities to the same extent and intensity as in the lower extremities, even in the most advanced stages of the disease. A strikingly analogous clinical condition is found in the two cases described above, with this difference that in them the lesion is confined to the motor tract alone, while in the anemia cases, the lesion is in postero-lateral tract. The first as well as the latest writers on this subject considered the syndrome as a subacute degeneration and sclerosis of the postero-lateral tract of the spinal cord in contra-distinction to the classical system-disease known as posterolateral sclerosis. In corroboration of their clinical contention they called attention also to the pathological differentiation. They found as characteristic the absence of shrinkage which is ordinarily found in the classical system disease, also the fact that the pathological lesion advances by gradual formation and subsequent coalescence of small foci. The existence therefore of a subacute form of combined sclerosis is authoritatively recognized (Déjèrine, Claude, Shaeffer, etc.)

The same consideration is applicable to the cases which present analogous clinical features in involvement of the motor pathway to the exclusion of any other system of fibers. It was mentioned above that the two cases described in this essay resemble and differ at the same time from the classical spastic paraplegia. They demonstrate the existence of a *subacute form* of primary lateral sclerosis. The course of the disease, the character of the symptoms are not all those of the classical primary lateral sclerosis and still the evidences are in favor of the pyramidal tract involvement. The development of the symptoms indicates that there is a considerable integrity of a large portion of the motor tract because of the absence of rigidity, and yet the lesion is sufficiently irritating to produce the increased knee-jerk and the extensor type of the plantar reflex analogous to those found in the subacute degeneration of the postero-lateral columns mentioned above or of the posterior columns (Marie, Crouzon and Déjèrine.) The literature on

subacute degeneration of one single tract in the cord is extremely meager. Two cases of that type were described by me in the Archives of Diagnosis 1921-1922, p. 131.

Conclusion

The interest of the present contribution lies not only in a special variety of affections of the spinal cord, but also and particularly so, in the occurrence of a condition which may be overlooked in the early phases of its development. When in the absence of traumatism or of a toxic-infectious state, of else of anemia, an individual gradually and progressively develops a weakness in the extremities, with or even without muscular atrophy, difficulty in station or gait, slight but distinct changes in the tendon or cutaneous reflexes, in all such cases a pathological state of the vertebrae or of the intervertebral spaces should be suspected. Radiographic examinations are then essential. Not infrequently vertebral rheumatism of a chronic character will be found. Osteophytic formations, nodules of various shape and form will be observed, obliteration of the intervertebral spaces, osteoporosis in the form of bright spots will be seen. It is true that in such cases there is frequently pain in the spine or in the gross articulations of the limbs before motor disturbances make their appearance. Chronic rheumatism is frequently a very painful affection. However, it would be a gross error to believe that this is always the case and that without pain there cannot be chronic rheumatism. Radiographic studies have shown that in many individuals who never or very slightly suffered, there were osseous lesions such as proliferation and rarefaction (Heberden's or Bouchard's nodules) which are ordinarily considered as characteristic of chronic rheumatism and which are identical with those found in rheumatism of long duration. This observation is correct with regard to rheumatism not only of gross and small articulations in the extremities, but also in the vertebrae or any other bony localization. It is therefore evident that in all cases of an oncoming weakness or of fully developed paresis of limbs with or without any atrophy, the cause of which is unknown or not manifest, radiographic studies of the bony structures and especially of the spinal column are indispensable. In this respect the extensive observations of André Lèri, particularly those which are concerned with the brachial plexus in chronic cervical rheumatism deserve special mention (Journal Médical Français, 1924, V. XIII; p. 273.) As to the pathological mechanism of disturbances in the extremities in cases of vertebral rheumatism, it is to be presumed that there is a radiculitis of an inflammatory or compressive character. Pain of course is always present to a greater or lesser degree, but it is not constant or permanent. Muscular atrophy is another manifestation which is frequent. A paretic condition is inevitable. Disturbances of objective sensibility of radicular distribution is to be expected. All these symptoms are the result of the passage of the roots composed of motor and sensory nerve fibers through the intervertebral foramina which are either inflamed or narrowed by the chronic rheumatism. A priori, such a clinical picture is to

be expected in every case of vertebral rheumatism. In reality, however, we have great varieties. In some cases the motor symptoms predominate, in others the sensory manifestations are conspicuous. In advanced cases there are evidences not only of involvement of the nerve trunks of the limbs, but also of the sensory or motor pathways in the spinal cord and of the cells of the anterior horns. There are also variations in the cause, duration, and rapidity of degeneration in the white matter of the cord. The affection described under the name of spondylose rhizomélique is another variety of the condition under discussion. Bechterew called attention to a limited kyphosis with ankylosis localized in the upper portion of the spine without involvement of the limbs. Strümpell under the name of "chronische ankylosirende Entzündung der Wirbelsäule" and Marie under the name of" spondylose rhizomélique" described a pathological condition of the spine with involvement of the limbs. Both types belong to the domain of polyarthritis deformans of the spine with secondary invasion of the roots, meninges and tracts in the spinal cord. Many intermediary forms belonging partly to one or the other of these types have also been described. The two cases presented above as well as those of the previous contribution (loc. cit.) are examples illustrating the variability in the localization of the lesion within the spinal canal and cord. They are also illustrative of the not infrequent existence of *"rheumatic root affections,"* of the importance of radiographic studies of the vertebral column and of the valuable assistance of the latter in our endeavor to determine the causative lesions in cases of an apparently mysterious and progressive motor paralysis. The suggestive features concerning the special variety of systemic disease of the cord in these cases have been already emphasized on the previous pages.

A Fatality Following the Intravenous Use of Ammonium Ortho-Iodoxy Benzoate*

By Bernard A. Manace, M.B. (Tor.), *Ann Arbor, Michigan*

AMMONIUM ortho-iodoxy benzoate has been introduced recently by Young and Youmans' (1) for the treatment of arthritis, and these authors have reported favorable results in patients presenting the chronic infectious and hypertrophic forms of the disease. It is closely related in chemical structure to the salicylates and has been extensively investigated in order to determine its physiological action. Since its introduction in the therapy of arthritis, a little over three years ago, Smith (2) has investigated the use of the drug in the treatment of arthritis and emphasizes the similarity of its action to that of the salicylaes. Although he obtained quite severe reactions, particularly following the intravenous route, no serious sequelae followed. More recently, Trauba (3) and Cottrell (4) have carried out similar investigations and report favorable results in the treatment of arthritis.

The purpose of this case report is to indicate that the intravenous administration of ammonium ortho-iodoxy benzoate is not without danger. I have had occasion to give the drug to a limited number of patients on the wards of the University Hospital. One hundred cubic centimeters of a one per cent aqueous solution of the drug were injected slowly into an arm vein. Invariably, the patients have had a more or less severe reaction, beginning usually after forty to fifty cubic centimeters had been administered. Patients would experience occasionally a burning sensation along the course of the vein, but the usual reaction was a severe burning in the eyes with lachrymation, smarting in the nose and tongue, and a sensation of tingling all over the body. Not infrequently chilliness or even a chill, with slight rise in temperature was experienced following the injection. Nausea and anorexia were frequently observed in addition. The unpleasant symptoms disappeared in fifteen or twenty minutes, and invariably the patient would feel better, although in many instances there was no appreciable change in the signs and symptoms of the arthritis. Venous thrombosis near the point of injection occurred in a few cases and sometimes extended along the full length of the arm, even involving a side branch of the vein.

Case Report

The patient, a single woman of fifty-seven years, weighing about ninety pounds, was admitted to the Medical

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Ward on September 2, 1927 complaining of swelling and pain in the joints, and presenting marked deformities. She had always enjoyed good health, but since the age of twelve years had had a discharging left ear, associated with buzzing, ringing, and impaired hearing. About sixteen months prior to this admission, she first noticed a slight swelling and pain in her ankles, and in a few days she was unable to put on her shoes. Then other joints became involved, chiefly the knees, shoulders, elbows, wrists, and small joints of the hands. By February, 1927, she was unable to stand, and since that date has been confined to her bed and chair. All of the teeth had been extracted without relief.

Physical examination revealed a middle-aged, white female, lying quietly in bed, whose development was fair, but nutrition poor. The skin was pale, and somewhat atrophic. The face was mask-like, full and rounded, with a marked malar flush. The pupils reacted to light and accommodation. Her chest was somewhat deep antero-posteriorly, showed fair expansion, was hyperresonant throughout, and a few fine, moist râles were heard at each base. No apparent abnormality in contour, size, or position of the heart was found. The heart sounds were regular, of good quality and somewhat rapid; no murmurs were heard. Blood pressure was 138/70 and the pulse was regular and forceful with a rate of one hundred per minute. Abdominal examination was essentially negative.

The extremities showed a very marked and advanced arthritis deformans with fixation of the joints in malposition. Both arms were held adducted to the thorax, with elbows flexed and immobile at an angle of ninety degrees. The hands were flexed at the wrists, with the fingers in extension and deviated to the ulnar side. The position of the hip joints at rest, was flexion at about forty-five degrees onto the torso. Both knees were fixed at a flexion of ninety degrees. The feet had a valgus deformity. Marked muscle atrophy was present in the arms, hands, legs and feet. There was very marked periarticular thickening about all joints, and crepitus could be elicited with passive motion.

The spine showed a marked rigid convexity involving the dorso-lumbar region.

Course in the Hospital

On September 27th, 1927, at 3:00 p.m., the patient was given 100 c. c. of one per cent "Amidoxyl" (ammonium ortho-iodoxy benzoate), using one of the small veins on the dorsum of the hand. The time required for administration was about thirty-five minutes. No apparent reaction followed, even the usual complaints of discomfort being absent. The patient was next seen by the interne at seven p.m., and nothing in particular was noted until about ten p.m. when she complained to the nurse about not feeling well. A few minutes after this she seemed irrational and her pulse became weak and thready. At 10:10 p.m., she quietly expired.

Post Mortem Findings*

Macroscopically all the blood vessels of the brain (meningeal, basal, choroidal), were considerably engorged. The meninges showed no thickening, or exudate. The brain substance was ede-

matous, and quite soft. No evidence of hemorrhage or thrombosis was found in any portion. The lungs, on cut section, revealed extensive congestion, more so on the right, but no definite pneumonic process was present. The liver and intestinal mucosa were markedly congested.

Microscopically, the above gross central nervous system findings were corroborated. The lungs were the seat of a marked acute exacerbation on a chronic congestion, associated with edema. Many small hemorrhages by diapedesis were noted. Advanced sclerosis involved the aorta, aortic valves and coronaries. The abdominal viscera showed chronic passive congestion.

The cartilages of the knee joint were considerably eroded, being replaced by granulation tissue, with some areas of organized fibrin. A chronic productive perichondritis with periostitis was present. The vertebrae showed osteoporosis with excess fatty marrow and some atrophy.

Examination at the site of injection failed to reveal any thrombosis or inflammation.

Comment

This is the first fatality which has been reported following the intravenous use of ammonium ortho-iodoxy benzoate. It is an indication that the drug should be used with discretion. It is well known that some people are sensitive to salicylates, and it is not improbable that patients will exhibit varying degrees of susceptibility to ammonium ortho-iodoxy benzoate. Such a fatality might have been avoided, if the initial dose of the drug had been small, i. e. 0.5 grams. To children and debilitated individuals it would probably be more conservative to give only 0.3 gms. as an initial dose. To those who have a known idiosyncrasy to salicylates, small initial doses should be administered because of the salicylate-like action of the drug. It would seem that subsequent doses should be increased with due caution, as in this patient the degree of symptoms during, and immediately following the injection of the drug, seemed to have no direct relation to its toxic action. This fatality has occurred after several hundred administrations of the drug in this hospital, and for that reason does not contraindicate its use in the presence of evidence for its markedly beneficial action. However, it does serve to demonstrate that size of dose to a given patient should receive due consideration.

*I am indebted to Doctors A. S. Warthin and N. W. Philpott for the pathologic report.

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The Embryohormonic Relations of the Suprarenal Cortex to Mesothelial Tissues

By Robert C. Moehlig, M.D. *Detroit, Michigan.*

In a previous communication, it was stated that the pituitary gland secretion has a selective action on mesenchymal tissues (1). The suprarenal cortex as a mesenchymal tissue is influenced by the state of the pituitary gland. In this communication it will be shown that the suprarenal cortex secretion has a selective action on *mesothelial* tissues. From the mesothelium are derived the following tissues

1. Striated muscle.
   (a) Skeletal.
   (b) Cardiac.
2. Sex glands, ovary, testis, etc.
3. Pericardium.
4. Pleura.
5. Peritoneum.
6. Serous layer of intestines.

A differentiation of the mesoderm into mesenchyme and mesothelium is not agreed to by all authors, some saying that this differentiation is unnecessary and classifying them under the head of mesoderm. But the clinical differentiation found in suprarenal cortex pathology makes this division preferable for clinical purposes.

The close relationship existing between mesenchyme and mesothelium is shown by the work of Lewis (2) who says: "The migratory mesenchymal cells in cultures of the embryonic chick heart show all stages of transformation from the bipolar and multipolar reticular cells to the flat mesothelial forms. One can actually observe this change in form. Such mesothelial cells seem to differ from the mesenchymal cells only in form and not in structure, indicating that mesothelium is to be considered not as a tissue differentiated from the mesenchyme but merely as a change or transformation in form."

Clark's (3) experiments also show the close relationship of the mesenchyme and mesothelium. His experiments indicate that mesothelium can be formed from the mesenchyme even in adult life.

Assuming then either that mesenchyme and mesothelium are identical or closely related, it becomes apparent from the previous article that the pituitary would have a controlling action on these mesothelial tissues, even without the intermediary action of the suprarenal cortex. The influence of the pituitary secretion on the sex glands is evident from both clinical and experimental work. Smith's (4) work on the induction of precocious sexual

maturity by pituitary homeotransplants is particularly interesting. Certain it is that primary pathology in the suprarenal cortex produces much greater pathological changes in mesothelial tissues than primary pituitary pathology. From these abundant clinical examples we may assume a selective action of the suprarenal cortex on this differentiated mesoderm, the mesothelium.

Starting with the striated muscle system we find both clinical and experimental evidence of the cortex influence. Biedl's (5) extirpation experiments on the fish species, skates and rays, are very interesting. In this species the suprarenal cortex and medulla are separate. Excision of the cortical tissue produced striking symptoms. These, which began as a rule, seven to eight days after operation, consisted of lessened movements and lifelessness. The spontaneous swimming around in the tanks became decidedly less. Fourteen to eighteen days after operation the muscular asthenia became so pronounced that the fish were unable to swim. They lay practically the whole day in a corner of the tank and took no nourishment. Stimuli failed to produce a reaction. Three weeks after operation they died with general prostration.

Elliott and Tuckett (6) concluded that the cortical portion has a definite relation to the skeletal musculature. They noted that the suprarenals increase with the development of the skeletal muscles, the increase affecting mainly the cortex. They also found that the cortex parallels the weight, whereas the medulla remains stationary. Severe exhaustion is always associated with hemorrhagic dilatation of the blood spaces in the cortex. In the kitten a movement of fat from the outer to the inner third of the cortex was produced by exhaustion. In a dog that had journeyed thirty miles all cortical cells were found to be vacuolized to a degree only seen in the fat bearing zone of the outer third of the suprarenal cortex.

Bardier and Bonne (7) studying the modifications produced in the structure of the suprarenals by tetanization of the muscles, found that these affected the cortex of the gland, not the medulla. Vincent (8) says that we do not know why the suprarenal cortex removal causes death, but it is possible that this is due to some defect in muscular metabolism.

Bauer (9) in discussing Biedl's experiments above quoted, says that the constancy with which cortical extirpation produces muscular asthenia in fishes and frogs up to the highest vertebrates, (Kahn's experiments on apes) points to a fundamental and vital function of the suprarenal cortex for muscle integrity. He goes on to say that animals and rats in particular who have accessory suprarenals and therefore are able to withstand bilateral suprarenalectomy without symptoms, show the suprarenal insufficiency first after muscular exercise. They fatigue easily, and may die suddenly (Albanese 9b, Mauerhofer, 9c.) Analogies occur in human pathology. Epinephrine cannot overcome this muscular asthenia.

Abelous and Langlois (9d) advance the view as does Vincent (8) that the suprarenal cortex neutralizes certain poisonous *muscular* products. Injections of suprarenal cortex extract fail to influence the muscular asthenia but

Bauer (9) says the reason is not to be referred to failure of simple neutralization of poisonous products by cortical substance but that we are dealing with a more complex phenomenon.

Hoskins (10) found that suprarenal extirpation often induces adynamia of from two weeks to permanent duration. Ergographic studies showed reduction of work capacity of individual muscles to one-sixteenth normal. Glycerine extracts of suprarenal glands (whole or cortex only), by mouth or subcutaneously, had no beneficial influence of voluntary activity. Bauer's remarks concerning these failures also applies here.

As reported elsewhere (11) in a series of cases in which suprarenal cortex medication was tried, viz. amenorrhea, muscular asthenia and one case of Addison's disease, I gave five hundred injections of a suprarenal preparation. The results were entirely negative. In this same series of cases I fed over a thousand five grain capsules of desiccated suprarenal substance. Beef suprarenal glands were cut in half and the cortex and medulla were grossly dissected from one another. The cortical portion was desiccated and prepared in the usual manner. Here, too, the results were entirely negative. It follows that with these methods suprarenal cortex medication is without effect.

Moore and Purinton (12) found marked asthenia in cats after removal of suprarenals.

Hartman (13) believes that it is generally accepted that the characteristic symptom in suprarenal insufficiency is muscular asthenia. Strehl and Weiss (14) observed that cats which were wild became very apathetic after suprarenalectomy.

Juice expressed from the muscles of suprarenalectomized rats when injected into other suprarenalectomized rats produces almost fatal muscular asthenia but has no influence on normal rats (Erni 9e). Erni (9e) found poisonous products in the muscles of suprarenalectomized dogs which were absent in normal animals. According to Elliott (15) the striped skeletal muscle is continuously under a tonic influence possibly in part derived from nerve impulses; but such a condition as myasthenia gravis proves that the tone is not altogether supplied from the central nervous system. He ascribes this tonic influence to the suprarenal cortex secretion.

Kühl (16) found that injection of epinephrine-free cortex extracts is sufficient to delay for hours the onset of the two chief symptoms of suprarenal collapse: muscular adynamia and respiratory disturbance. Epinephrine and other organ extracts did not produce this effect, showing that the cortical extract contains a specific internal secretion. Castaldi (17) found that feeding suprarenal cortex of the ox to the very young guinea-pig favors the formation of muscle.

Clinically of course, we are well aware of the outstanding symptom of *muscular asthenia* in Addison's Disease. From what has been shown previously it would seem safe to assume that the muscular asthenia of Addison's disease is cortical in origin. In stating this I am well aware of the experimental work done in regard to

epinephrine as a remedy for muscular asthenia.

Since the cardiac tissue is a specialized skeletal muscle, it likewise shares in the muscular asthenia. At postmortem the heart is usually atrophic and the myocardial symptoms common in this disease may be assumed to result from cortical damage. The general impression seems to be that because the medulla gives off epinephrine, a blood-pressure raising principle, that in Addison's disease low blood pressure is due to a diseased suprarenal medulla. On the contrary, the evidence points to a loss of cortical tissue as the etiological factor, and even the low blood pressure may be due in part to the muscular asthenia. I do not, of course, belittle the medullary involvement in Addison's disease.

A recent comment in the J. A. M. A. (18) states that the suprarenal glands are indispensable to life. "At present the preponderance of evidence favors the suprarenal cortex as the portion of the structure that is responsible for the genesis of the essential factor."

Concerning sex gland hypofunction and hypoplasia, there is much evidence connecting these conditions with the cortex of the suprarenal gland. MacKenzie (19) says "Probably the interrelationship of the suprarenals and the sexual glands has been demonstrated most clearly."

In Addison's disease Kyrle (20) found deficient spermatogenesis and degenerative changes in the interstitial glands. The clinical manifestations of this state in Addison's disease are the impotence, sterility and amenorrhea.

Leupold (21) found a close relationship existing between the suprarenals and testes. He found that when the suprarenals contain much fat the quantity of fat in the testes is also high. The testes contain less cholesterol than do the suprarenals and when cholesterol diminishes in the testes and the suprarenals it is generally first decreased in the former. He believes this proves that the suprarenals have a "higher" function than the testes.

Podvissotzsky (22) and Mulon (22) both called attention to the resemblance of the ovarian cortical cells to the suprarenal cortex. Mulon (22) believes that the corpus luteum of pregnancy is a temporary suprarenal cortex.

Elliott (15) says that there is reason to believe that suprarenal cortical tissue is embedded in the sex gland itself, giving rise to the lutein cells of the ovary or the interstitial cells of the testis. Serdivuklov's (23) experiments showed that there exists a functional interdependence between the suprarenal cortex, the parenchyma of the corpus luteum and the interstitial gland of the ovary.

Hoskins and Hoskins (24) found hypertrophy of the testes and ovaries in white rats who had been fed desiccated suprarenal substance. Vigor of reproduction is reduced by partial suprarenal extirpation. (Vincent (8)).

Suprarenal cortex hypofunction in relation to the other mesothelial tissues such as pericardium, pleura, etc., is of course not so important. I can find no conclusive evidence concerning this. A smooth glistening peritoneum

is occasionally mentioned in Addison's disease but on the whole the serous layers do not receive any prominent notice.

Proceeding to hyperfunction of the suprarenal cortex in its relation to *muscle tissue* and *sex glands*, we find much to support this embryohormonic relationship.

Suprarenal cortical tumors of a hyperfunctionating type in the young produce marked changes in the sex development and skeletal muscle system. Female infants with this type of hypernephroma menstruate, are precocious sexually and are usually muscular and strong. Infant boys have premature development of the genitalia, and are equal in size and strength to boys at the age of fifteen and sixteen years. They are know as "Infant Hercules".

Linser (25) first described tumors of the suprarenal cortex accompanying precocious sexual maturity in children. Bulloch and Sequeira (26) reported further cases and included a study of cases previously reported. Glynn (27), Hoag (28), Collett (29) and recently Gordon and Browder (30) have reviewed the literature and added cases of their own. The case of suprarenal cortex tumor reported by Gordon and Browder (30) showed a "Herculean" build.

Pseudohermaphroditism is frequently associated with hyperplasia of the suprarenal cortex. Marchand (31) who first reported such autopsy findings found colossal hyperplasia of the cortex associated with a large accessory suprarenal.

Jump (32) says that at present we are justified in believing virilism and hirsutism are caused by increased functioning of the suprarenal cortex, varying in degree and due in some instances to neoplastic growth of the suprarenal cortex.

Riddle (33) believes that it is extremely probable that the suprarenals regularly and greatly enlarge in close relation to the time of liberation of the ova from the ovary.

Schief (34) basing his work on 1,227 autopsies, found that there is a distinct increase in the suprarenal weight with increasing stature and the testes show a parallel increase in weight with an increase in the adult suprarenal. These findings of Schief support the evidence given in the previous communication, that the pituitary gland, influencing the bone development and stature, likewise influences the suprarenal cortex and sex glands.

There is no need to cite further evidence that the suprarenal cortex is related to sex glands for this is accepted by most authors. From what has gone before, an obvious embryohormonic relationship exists between the pituitary gland, the suprarenal cortex, skeletal muscle and sex glands.

Summary

The suprarenal cortex secretion has a selective action on mesothelial tissues.

The important mesothelial tissues, sex glands and skeletal muscle are influenced by the state of the suprarenal cortex.

Both the mesenchyma and the allied mesothelium through the suprarenal cortex are influenced by the pituitary gland.

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Case of Coronary Occlusion With Complete Heart Block

Interesting Electrocardiographic Findings

By Louis H. Sigler, M.D., *Brooklyn, N. Y.*

THERE are several features in the following case which make it of sufficient interest to be put on record. The correlation between certain of the electrocardiographic findings and the clinical manifestations; the resemblance of such findings to those of experimental production of coronary closure, as reported by some workers; and, their occurrence in a pulseless individual, with heart sounds practically inaudible, are all factors worthy of note.

The case is that of a Hebrew, male, 70 years of age, retired grocer, whose past history is essentially negative, except for "stomach complaints" for the past twenty years, consisting of constipation, occasional "heartburn" and epigastric discomfort. There were no precordial pain, dyspnea, palpitation or other symptoms referable to the heart, at any time. He was always in the habit of walking fast without the slightest discomfort, up to the onset of the present illness. He never smoked nor drank any alcoholics, and his habits were fairly regular.

On January 18th, 1928, while taking a bath, he suddenly collapsed. On recovering consciousness several minutes later, he complained of a most agonizing pain in the left precordium, radiating to the left shoulder and arm. Associated with the pain there was marked dyspnea, with a sense of impending dissolution. He was pale, and his entire body was covered with a cold perspiration. The condition lasted about eight hours, when he began to feel better and in twenty-four hours the pain practically subsided, leaving him with only a dull ache. Generally he likewise felt at that time well enough to leave his bed, against the advice of his doctor.

He continued to feel well, and was up and about for seven days. He even did some work around the house without any discomfort, except for some dull ache in the precordium.

I was summoned for the first time on January 25th, 1928, at which time he had an attack similar to, but more severe than that of the 18th. The pain at this time was most severe in the right hypochondriac region. On examination I found a male, about seventy years of age, lying in bed in great shock, and suffering with in-

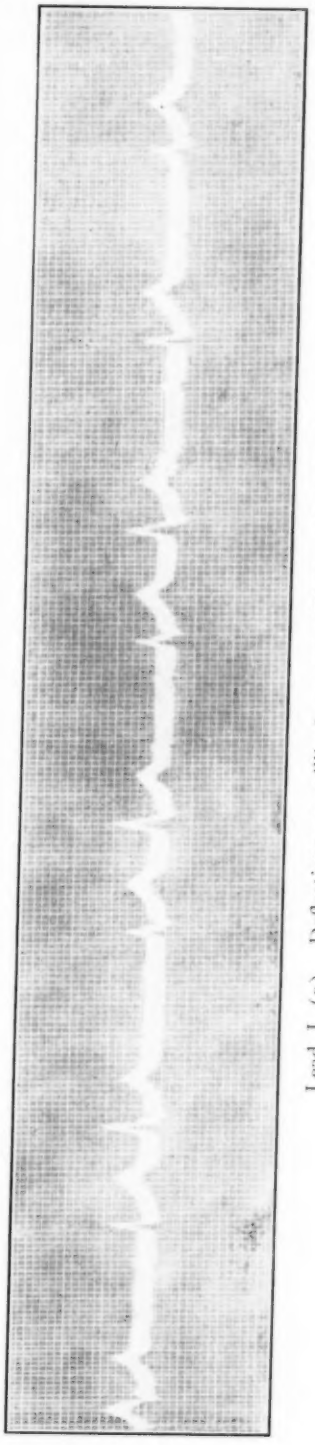
tense, agonizing pain. His entire body was pale and covered with a cold, clammy perspiration. His face had an ashen-gray appearance. His pupils were dilated and responded sluggishly. He had marked arcus senilis and general arteriosclerosis. His lungs showed signs of congestion, and heart percussed out was enlarged to the right and left. The heart sounds were very faintly audible and rate was slow. The rhythm was markedly disturbed and, together with the almost inaudibility of the sounds, the exact rate could not be made out. He was pulseless most of the time, except that now and then a very thin, thread-like pulsation, was felt at the radials. He had marked rigidity and great tenderness in the right upper quadrant of the abdomen, and, as said before, he pointed to that area as the seat of his greatest pain.

About two hours after the onset of this intense suffering he gradually began to lose consciousness, would doze off for a few minutes, only to be disturbed by the great intensity of pain which would awaken him with a groan. An hour later he lost complete consciousness, assumed Cheyne-Stokes respiration and died in twenty minutes.

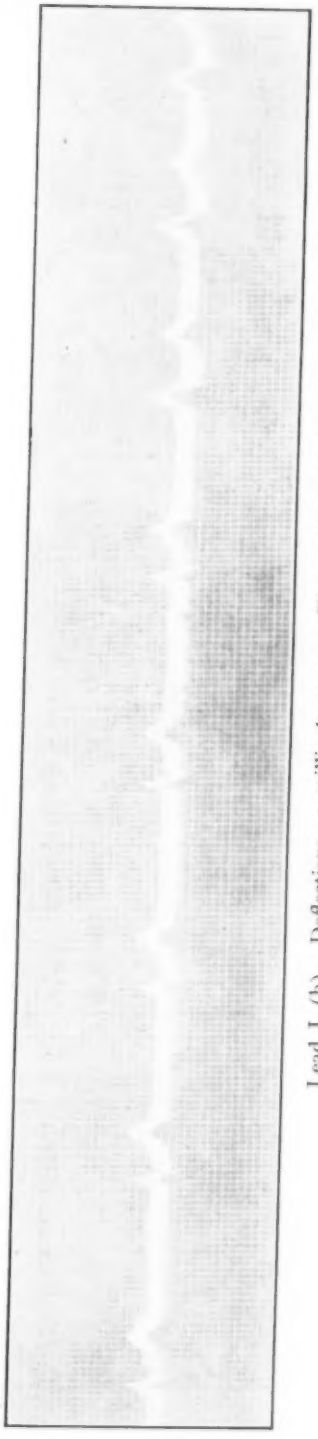
The electrocardiographic tracings, taken one half hour before death, show complete auriculo-ventricular dissociation. The auricular rate is about 120 and the ventricular rate, including the aberrant complexes, about 48. The auricular waves seem to be of normal sinus origin, and recur at regular intervals, disfiguring some of the ventricular complexes, marked especially in lead II. The ventricular complexes are of three distinct types—a normal supraventricular and two aberrant, originating in two different foci. These assume at times a bigeminal-like character, best seen in lead I (a). At other times, groups of three or more such complexes, starting in the same focus, occur either in regular succession, as seen in lead III, or group themselves in coupling as seen in lead II. There is marked notching in the supraventricular complexes in lead I, and slurring in lead III. The T-wave is interesting. In lead I it is positive, and in the normal complexes it is as high as the R-wave. Its ascent starts from the S-wave and runs directly upwards, not preceded by any iso-electric interval. In leads II and III it is negative. In both leads it starts from the descent of R before it reaches the base line and has a tendency to run somewhat horizontally and downwards before assuming the negative phase, inscribing, in so doing, some curvature. The aberrant complexes seem to have similar T-waves. The complexes are greatly disfigured from time to time by the superimposed P-waves, whenever such waves appear. Both, the supraventricular and aberrant complexes are of low voltage.

Comment

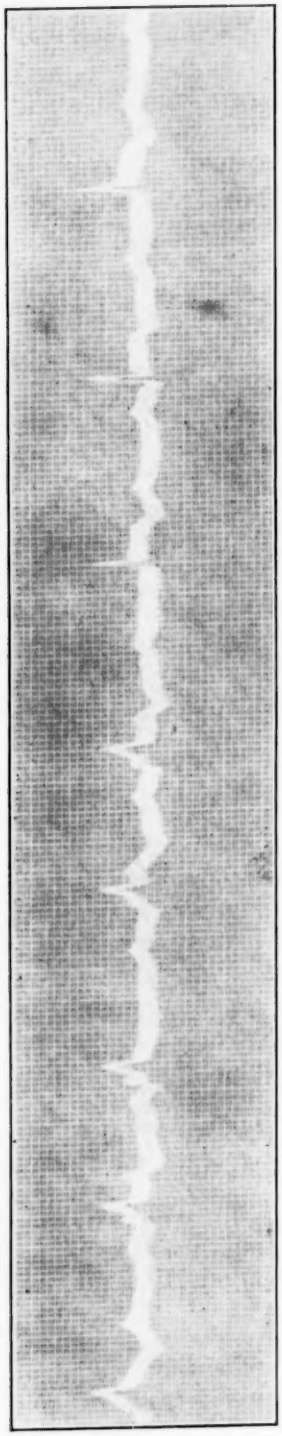
We have here an individual giving no previous history or symptoms of cardiac disease, who suddenly developed an attack presenting a typical picture of coronary closure, followed seven days later by a second, similar but more severe attack. The first attack, although very severe, produced no subsequent symptoms of cardiac decompensation, as shown by his behaviour during the week following the



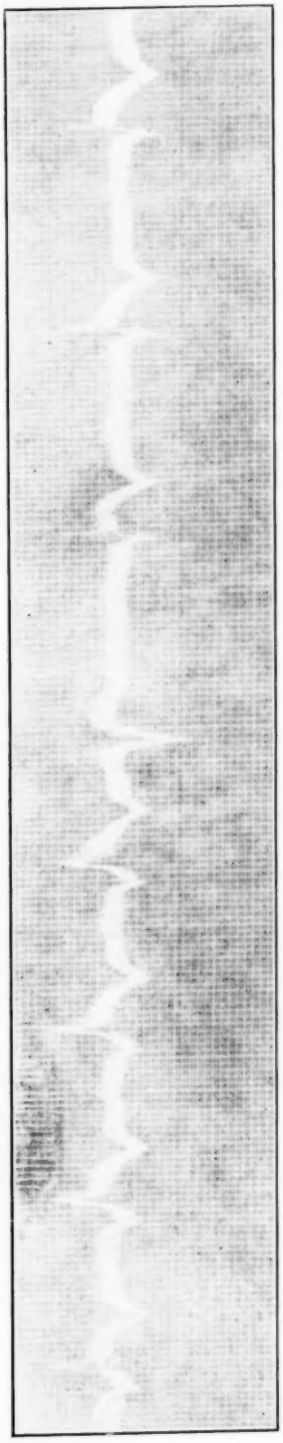
Lead I (a). Deflections—1 millivolt=1 cm. Time—1/5 and 1/25 sec.



Lead I (b). Deflections—1 millivolt=1 cm. Time—1/5 and 1/25 sec.



Lead II. Deflections—1 millivolt=1 cm. Time—1/5 and 1/25 sec.



Lead III. Deflections—1 millivolt=1 cm. Time—1/5 and 1/25 sec.

attack. It has, however, made its mark on the myocardium in the form of degenerative changes, as evidenced by the electrocardiographic findings.

The findings telling the tale of the first attack are most probably the complete A-V dissociation and the negative T in leads II and III. In the absence of any evident symptoms of cardiac disease previous to the first attack, it is reasonable to assume that such defects were not present before. That these developed at the second attack is likewise not probable. For, complete block to set in, a certain amount of degeneration of the junctional tissues would be necessary, which would require much more than two hours to develop. Also, the negative T in the two leads is an indication of degenerative myocardial changes of at least one day's standing, conforming with the experimental evidence brought forward by Smith (1). This author ligated various parts of the coronary arteries in dogs, and found a constant change in the T-wave from positive to negative. Soon after ligation this wave was more prominently positive than the normal, which increase in positivity was explained by Pardee (2), quoting the experiments of Eppinger and Rothenberg, as being due to an initial increase in chemical activity following the onset of destruction of tissues. In twenty-four hours the T-wave became negative in one, two or all leads, and the amount of negativity was proportional to the size of the artery ligated, and its supply to the apex. This marked negativity persisted three to four days and gradually became less, so that on the seventh day, it became again positive in one lead.

Some clinical reports published by Smith (3) later, showed a resemblance of the T-waves in some cases to those of his experimental findings.

Just as the first attack in our case under discussion left its electrocardiographic imprint, so did the second attack. In the latter, we have the premature ventricular contractions occurring singly and in groups, and conforming to the laboratory findings of Lewis (4) and of Smith. Both found, in independent experiments, that within a few minutes to 1½ hours following the ligation of some portions of the coronary arteries, premature contractions set in which in some cases developed into paroxysmal tachycardia. The prematures run in groups of two, three to five or more, and gradually diminish in number after some time.

Although the clinical and electrocardiographic findings in this case harmonize, in the face of experimental evidence, there is a possibility that the latter findings might have been the result of a gradual, degenerative process of many years standing. The presumption that the patient was suffering from myocardial degenerative changes incident to sclerosis of the coronaries with gradual narrowing of their lumina and shutting off of the blood supply to the myocardium, may be true in the face of the usual post mortem findings in such cases. Even in the absence of definite cardiac symptomatology in any case previous to an attack of coronary closure we could not absolutely rule out previous cardiac disease. Subjective symptoms

presented in any history are purely individual, and vary greatly with the susceptibility of the subject. The findings in this case, however, are so strikingly interpretative of occurrences of recent closures, and resemble so closely the experimental data, that we may assume them to be part and parcel of the attacks.

SUMMARY

Case report presenting two attacks with a symptomatology which clinically is interpretive of coronary closure. The electrocardiographic findings, 30 minutes before death, not only confirm the diagnosis but seem to present evidence of each separate closure which occurred at intervals of seven days. The findings also conform with those obtained in the laboratory by varoius workers.

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Epilepsy Late in Life

By Oliver T. Osborne, M.A., M.D., F.A.C.P., *Professor of Therapeutics, Emeritus, Yale University, New Haven, Conn.*

THE paper of Doctors Riesman and Fitz-Hugh, Jr. on epilepsy in the Annals of Internal Medicine for November, 1927, deserves more than a passive reading. This important subject has not been sufficiently discussed, and we are indebted to these clinicians for so ably presenting it.

Besides such cases as occur from arteriosclerosis and endocrine dysfunction, I believe the majority of these cases are associated with mouth infection. Very few persons after forty have healthy mouths; most of them are carrying devitalized teeth, crowns, and often bridges, and pyorrhea alveolaris is very common in persons of this age.

If mouth infection plays an important part, as has been shown, in many types of insanity, it could easily have a causative relation to these late epilepsies. Many thyroid disturbances are due to absorption from infections of the mouth, either teeth or tonsils. This is a clinical fact that can be demonstrated by the removal of these mouth infections and the subsequent marked improvement and sometimes cure of this thyroid disturbance. Whenever a thyroid gland is disturbed by mouth infection I believe the parathyroids are always also disturbed; in fact, many symptoms of thyroid disturbance are really caused by parathyroid disturbances, and I believe that parathyroid disturbance sometimes, if not frequently, plays an important part in epilepsy. Certainly, disturbance of the parathyroids upsets calcium metabolism, and calcium insufficiency is a very positive cause of nervous irritability. Therefore in every case of late epilepsy the mouth should be carefully studied and every source of infection removed.

Also as noted by Riesman and Fitz-Hugh, some of these epileptic patients have glycosuria or a real diabetes, and I have frequently found that in mild glycosuria, in which slight modification of diet would remove the sugar from the urine, that the eradication of alveolar pyorrhea would allow all of these patients to improve. In other words, they could take more liberal diets without glycosuria.

I have occasionally found that epileptic attacks develop in women at the menopause. Such cases belong to the endocrine dysfunction group of Riesman and Fitz-Hugh. In such cases when the endocrine disturbances have been treated from the endocrine standpoint the attacks have been cured. If there is hypertension at the menopause, corpus luteum treatment is fre-

quently successful in reducing the blood pressure. Any infection or other cause of disturbance or growth of the pituitary gland may be a cause of epilepsy, as epileptic attacks are not infrequent in acromegaly.

Serious eyestrain, a cause that has been much ridiculed, can occasionally cause epileptic attacks, and these epileptic attacks may be cured by proper glasses. Sometimes these cases of eyestrain occur at the period when presbyopia begins to develop. An epilepsy beginning at this age from this cause may be stopped by proper glasses, if the cause is noted and treated early.

We all recognize the peculiar cyclic habit of the nervous system, and similar to asthmatic attacks and periodic headaches, epileptic attacks, once established, may persist, whatever the cause, in spite of proper treatment.

Editorial

Second Annual Exhibition of Works in the Plastic and Graphic Arts By American Physicians Under the Auspices of the New York Physicians Art Club

There has just been held in the exhibition rooms of the beautiful new building of the New York Academy of Medicine, the second Annual Exhibit of original works in the plastic and graphic arts by contemporary American physicians. The first one, held last year, was most successful, not only because of the importance of the exhibit from technical and artistic points of view, but because it demonstrated in the first place the existence in the American medical profession of a considerable body of individuals interested practically in the creation of beautiful things. That exhibit aroused great interest throughout the country, as shown by numerous printed notices of it. It served to crystallize scattered and sporadic efforts at artistic expression by medical men in other parts of the country, as was made evident by the fact that during the year several other physicians' art exhibitions were held in other cities, and by the numerous new exhibitors in this year's show. This movement, however, is but a small beginning in bringing to the light this cultural aspect of the medical man's mental and spiritual makeup. As we have written elsewhere the psychology of the medical life, demands intellectual recreations of a release nature, and such release from the depressing facts of daily professional contacts with abnormal life can be found only in the quest of beauty in nature and in creative art. Throughout the country there are numerous practitioners who seek solace in various attempts at creating something they do not possess, but which in the joy of creation offers that necessary and much-desired psychological catharsis. Without this renewal of outlook there is no human mind capable of retaining that equilibrium of mental and spiritual processes essential to happy and successful living. One, therefore, notes with great pleasure and optimism such evidences of medical culture as those seen at the New York Academy of Medicine. The exhibit was arranged by the New York Physicians Art Club, of which Dr. I. S. Hirsch is the President, Dr. H. S. Patterson the Vice-president, Dr. H. A. Bancel the Secretary and Dr. Herman Fischer the Treasurer. It was well-arranged and well-lighted, in the large room on the ground floor to the right of the entrance in the new Academy building on upper Fifth Avenue. The foreword to the catalogue was written by Dr. George D. Stewart, President of the American College of Surgeons. The catalogue listed eighty exhibitors with two hundred and eighty exhibits. These represented many fields in the

plastic and graphic arts: paintings in oil and water color, etchings, wood cuts, book plates, sculpture, wood carving, marquetry, miniatures, book bindings, architecture, lettering, relief map making, etc. This catholicity of expression gave an especial atmosphere of interest to this collection. One got from it what one does not always get from the exhibitions of professional artists. These were real individual expressions of what attracted the artists', the physicians', to be more exact, personality, and for this reason, to a fellow worker in medical science, the exhibit had a living sense of individual personalities. Here, one felt, were men and women doing for fun, and getting a lot of fun out of it, just the things that appealed to them, that they wanted to recreate and as they wanted to. For this reason exhibitions of amateur art are always more refreshing and satisfying than those of the average professional kind where commercial disposal of the product is too often loudly proclaimed and felt. Matters of style, technique and vogue are of less importance here. What matters is what appeals to the artist as beauty, and his effort to reproduce that beauty. Here is one man interested in waterfowl and he recreates their artistic significance to him; another one sees the elusive beauty and mystery of the sea and ships and strives to hold it; others feel the beauty of mountain tops and upland pastures, of trees and flowers, the human form, houses, phases of human life—it matters not just where beauty is seen and caught—what does matter is that these men and women active in a daily professional contact with the ugliness of disease, feel this beauty, pursue it and attempt to recreate it. This is the highest form of culture. This is the real artists' spirit. Deficient in technique, crude in execution some of these efforts may be, but the spirit of individual expression is the thing that counts. As a matter of fact, it is wonderful how clever most of these efforts are, and how well done. A comparison with professional work leads to no too-condemnatory attitude. The technical methods employed are usually straight forward and simple; there is but little attempt at fooling with abnormal modernistic freakish modes. Still, even this might be done for fun also; but the fact remains that the great majority of these medical artists are primarily concerned with the beauty of nature and the human form, and attempt in the simplest and most honest mode to recreate it. Of the things that appealed especially to the writer may be mentioned "The Lonesome Barn" by John Howard Allen of Portland, "A Landscape" by Frederick Adams of Seattle, "Old Veterans" by Herman Fischer of New York, "Old Bridge" by Leigh H. Hunt of New York, "Texas Blue Bonnets" by Sallie W. Miller of Slaton, Texas, "A Bit of Norway" by J. R. Nilsen of New York, "Hill Pasture" by R. C. Larrabee of Boston, "Olympic Mountains" by F. W. Southworth of New York. These preferences, however, are probably the result of the personal appeal made by the subjects as well as by their successful reproduction. It was characteristic of this exhibit that the great majority of the artists drew their inspiration for creation outside of their professional field. There were few attempts at purely scientific draw-

ing or illustration, or at artistic representation of material from the medical life and professional contact with human life. Not that these do not offer rich fields for artistic expression and creation; but the writer was interested in the fact that appeared very patent to him, that the material chosen for art subjects in this exhibit were true release subjects. Perhaps for the greatest recreative good to the medical man this getting outside of his professional field offers the highest values, if he works only in this one field of recreation. The farther removed from vocational atmospheres, perhaps the greater cultural good for the man of medicine. It is to be hoped that this movement for exhibitions of art works produced by medical men will extend throughout the country, and that interested groups throughout the larger cities, at least, may be incited to concentrate and crystallize this aspect of the medical man's cultural life. Incalculable good to the profession must come out of such efforts, which in the end lead to that most desired result of all—the liberal education of physicians.

Abstracts

Physiological Factors in the Genesis of Gallstones. Fourth Ludvig Hektoen Lecture on the Billings Foundation. By PEYTON ROUS (The Proceedings of the Institute of Medicine of Chicago, April 15, 1928).

Knowledge concerning gallstones is just emerging from the observation stage. Experiment has shown that the calculi developing out of the bile of laboratory animals differ essentially in their constitution from human gallstones. It is the human problem that is important; and it might seem that animal experimentation on gallstones is a waste of time, were it not for the fact that human biliary calculi are to a very large extent the product of physiological activities that can be studied advantageously in animals. These physiological activities are the constants of the gallstone situation as contrasted with the variables such as infection, dietary habits, tight lacing and the like. The variables are subject to alteration as situations and customs alter. But neither endeavor nor whim will enable an individual to go free of his physiological actions and responses. The riddle of cholelithiasis resolves itself into two questions, how stones begin and why they grow. Observation has shown that biliary calculi cannot in general be explained as merely the result of deposition out of a supersaturated bile upon any nucleus that comes to hand. A great variety of formed sediments which might conceivably serve as the beginning of stones is to be found in human gall-bladders, but their effect in this relation is to all intents and purposes nil. For the nucleus of the great majority of human stones would seem to be a very special thing. The majority, or all, of human stones have a pigmented center consisting of calcium bilirubinate. Whence comes this nucleus and under what conditions? It is possible to follow the early development of gallstones out of the sterile bile of dogs and thus to gain knowledge bearing upon the problem. While dog stones differ from the ordinary run of human stones, being made up almost entirely of calcium carbonate, as seldom happens in man, their nuclei consist of the same material, calcium bilirubinate. This substance does not occur in normal bile despite the presence there of the ingredients necessary to its formation. Day to day study of the dog has shown that when the animal is seriously ill from any one of a number of various causes, bilirubinate often comes down out of the liver bile in the form of minute brown granules. Under such circumstances the granules may appear in veritable showers, and during the weeks that follow, stone formation takes place on them, as it does not, in general, on such other formed sediment as may be present. Only when there are considerable accumulations of cell debris exposed to the bile current does stone formation occur in the absence of bilirubinate nuclei. The gradual development of carbonate stones in the midst of such debris may be thought of as a variant upon the calcification so frequent in dead tissue elsewhere throughout the body. Carbonate stones occasionally arise under similar conditions within the human biliary tract. From the observations on dogs it may be inferred that some intercurrent illness, by bringing about the conditions for a precipitation of calcium bilirubinate from the bile, will act to provide during the lives of most individuals more than sufficient potential nuclei for stone formation. This being the case, it seems amazing that stones do not occur more often under natural conditions. For in comparison with the number of possible nuclei stones are rare. Many kinds of foreign bodies have been introduced into the biliary tract of animals in the attempt to produce

stones, but as a rule without success. Such bodies, like the bilirubinate nuclei, act merely to pull the trigger of calculus formation, but usually the gun is empty. It is in the circumstances surrounding the development of calculi, not in the occurrence of suitable nuclei for them that the real problem of gallstones lies. The simplest possible stone formation would be by deposition from a supercharged bile. Such a deposition is probable in the case of the solitary cholesterol stone of man, and that a diathesis may be responsible for the bile character in some such instances and dietary habits in others. The question has arisen whether pure pigment stones—stones consisting of calcium bilirubinate—are not diathesis stones as well. One can suppose a persistence of the initial derangement which leads to a deposition of calcium bilirubinate nuclei out of the bile has much to do with their formation. In this relation it is worth while to realize that about 60 per cent of patients with congenital hemolytic jaundice show gallstones at autopsy, bilirubinate concretions which have formed out of biles abnormally loaded with pigment, and at an age when cholelithiasis is notably rare. If a supercharged bile will explain the occurrence of a small proportion of human stones, what is responsible for the more frequent ones? Biliary stasis alone is not sufficient, nor stasis and a foreign body, nor even stasis, foreign body and infection are sufficient to produce animal stones, unless the last gave rise to a low grade chronic cholecystitis, and even this last was far from being a regular occurrence. Animal experimentation has sufficed to show, that although human and animal stones differ in constitution, the conditions under which they arise are the same in both. The normal gall-bladder acts to render its contents acid; the more concentrated the bile the more acid, and the less likelihood of stone formation. It might be inferred that if the gall-bladder is prevented from rendering its bile acid, stones will form. There exist in the literature observations strongly suggestive of this. However, no adequate study of the reaction of the biles associated with human stones has been made, and one cannot say whether a functional failure in this relation on the part of the organ will result in cholelithiasis. The possibility suggests itself that the loss of one function and the retention of another by the organ may have even more baneful consequences than if both are wanting. This question of the immediate cause of gallstones cannot be settled with our present knowledge. Speculation is idle, and the question must be left to future investigation.

Observations on Urobilinogen in Urine. By JOHN B. DEVINE AND G. O. BROWN (Proc. for Exper. Biol. and Med., March, 1928, p. 502).

Urobilinogen of the urine was estimated quantitatively by the method of Gerwen. Definite increases in urinary urobilinogen were found in cases of liver pathology. Increased values were also found in some cases of diabetes mellitus, most of which showed some suggestive evidence of an accompanying liver pathology. This was proven in two cases coming to autopsy, one of which showed cirrhosis and the other marked passive congestion of the liver. Increases were also found in some cases in which no definite evidence of liver pathology could be found. Active cases of pernicious anemia showed this finding. Cases of severe nephritis frequently showed increased urinary urobilinogen. It is questionable whether this should be attributed to a possible accompanying liver lesion or to increased renal permeability to this substance. Nephritic cases with a high urobilinogen output are usually accompanied by anemia. A similar high urinary pigment output is noted in other secondary anemias of obscure etiology. This suggests that loss of pigment may play some rôle in the production of the anemia. A few cases of renal glycosuria were found to have high values for urinary urobilinogen. This may also be due to increased renal permeability. The occurrence of increased output of urobilinogen in urine of cases in which no definite evidence of liver pathology could be discovered, impairs the value of the use of this reaction as a test of liver function.

Carcinoma of the Esophagus. By EDWARD S. CLAYTON (Surg., Gyn. and Obstet., Jan., 1928, p. 52).

This is a study of 41 cases of esophageal cancer seen in the last 5 years at the Philadelphia General Hospital. The average age of these patients was 60 years and 6 months, and the great majority were in their sixties. 39 were males; 8 occurred in the colored race. Cancer of the esophagus forms a little more than 5 per cent of all cancers. It is a lesion occurring for the most part in males. Symptoms occur very late, the average duration of life after the onset of the first symptoms being about 7 months. The most common symptom causing the patient to seek medical aid is difficulty in swallowing, while dysphagia in its true meaning, painful swallowing, is very common. About 75 per cent of esophageal carcinomas metastasize, and the cause of death most commonly is an intercurrent bronchopneumonia. The lesion occurs most commonly at the level of the bifurcation of the trachea at the point where the esophagus is crossed by the left bronchus. The second most frequent situation is about the point where the esophagus passes through the diaphragm. These are the points where normal anatomical constrictions of the esophagus are most marked except at its beginning. There is no relation between the duration of symptoms or the size of the local lesion and the extent of metastasis, for some of the smallest lesions give rise to extensive metastasis, while, on the other hand, some of the most extensive local lesions give rise to very little, and some to no metastasis. The depth of the esophageal wall involvement does not have any relation to distant metastasis, but does to local extension. The most important factor with the duration of life and the extent of metastasis is the degree of malignancy of the individual growth, which can be determined by the microscopical examination. The position in which the cancer occurs in the esophagus does not have any relation to the extent of metastasis, but does have some relation to the direction of metastasis. Cancers of the upper third metastasize to the glands in the superior mediastinum or deep cervical glands. Those of the middle third commonly involve the lymph glands around the bifurcation of the trachea. They metastasize below the diaphragm less commonly and less extensively than do those involving the lower third. Cancers of the lower third most commonly metastasize below the diaphragm through the coeliac chain. It seems unlikely that radium will have any place in the treatment of esophageal cancer, for the wall is involved deeply, and in most instances if the cancer cells could alone be picked out, perforation would occur, and the patient die of empyema, abscesses or some chest complication.

Principal Causes of Illness in Typical American City (United States Public Health Service, March 26, 1928.)

Public Health in a given community depends upon the personal health of each individual. Health officials generally have recognized, according to Surgeon General Cumming of the United States Public Health Service, that although a great deal is accomplished by means that deal with community conditions, yet the individual is the foundation upon which the public health is built. In order to know what diseases must be guarded against it must first be known what diseases are present.

Not only the causes of death but the causes of ill health as well are of great importance to health officers and physicians in their scientific searching for causes and conditions in their preventive work. Of far greater importance than death rates and life table expression is a view of the health situation depicted by physical impairments as revealed by competent medical examinations and by morbid conditions as ascertained by adequate records of sickness.

With this thought in mind a study was conducted by the Public Health Service extending over more than two years in a city regarded as a typical American small city in one of the eastern States. The information obtained through this study is of great interest to the general public as it shows clearly what diseases are most prevalent in the general population.

The city in which these studies were conducted may be said to be typical of many other cities of its size in the eastern section of the United States. The principal object of this study was a record of illnesses that were experienced by a population group com-

posed of persons of all ages and both sexes, and in no remarkable respect unusual. The records of illnesses obtained were of illnesses as reported to experienced investigators. The reports were made by the household informant, usually the wife, either the sickness as experienced by herself or as she observed it in her family.

The rate of sickness from colds and bronchitis was the highest, being annually 418.6 per 1,000 persons. Influenza and grippe came second with a rate of 143.2 per 1,000; diseases of the digestive system were 96.5 per 1,000; tonsillitis and sore throat 65.7; confinement and other puerperal causes 46.9; diseases of the nervous system, including headaches, 44.1; accidents and other external causes, 39.5; measles 34.2; whooping cough 22.6; rheumatism and lumbago 21.8; heart and other circulatory diseases 18.3. The list contains ten or eleven more items and concludes with hay fever and asthma which is shown to have caused 5.8 cases of sickness each year per 1,000 persons.

From this study fairly accurate records of real illnesses were secured. As a matter of fact less than 5% of the illnesses of exactly stated duration were recorded as one day or less in duration; nearly 80% were three days or longer, and 60% were eight days or longer in duration. Approximately 40% were not only disabling but caused confinement to bed. It is evident, therefore, that in the main the illnesses recorded were more than trivial in their character, in spite of the fact that in some instances mere symptoms were given as diagnoses.

There are certain facts from this study that stand out with particular significance. First, the extraordinary high incidence of sickness shown in early childhood was a rather surprising result. Illness was far more frequent under 10 years of age than at any other time of life. Second, the interesting suggestion was afforded that the average individual is more free from illness in the age period 15 to 24 years. Thereafter sickness becomes more frequent as age advances, and it may be added, upon the basis of other studies as well as these, that sickness becomes more severe and more frequently fatal.

The picture given by the record of sickness according to causes, or more precisely, according to the kind of sickness is in sharp contrast to that given by causes of death. Respiratory diseases and disorders account for 60 per cent of sickness as against 20 per cent of deaths. The general group of "epidemic, endemic, and infectious" diseases account for eight per cent of illness, whereas only about 2 per cent of the deaths were due to this group. Digestive diseases and disorders caused 10 per cent of the illness as against 6 per cent of the total deaths. On the other hand, the group of general diseases (which includes cancer, the diseases of the nervous and circulatory systems and the diseases of the kidney and related organs) were relatively much more important causes of death than of sickness. The diseases of the heart and blood vessels show the sharpest contrast—24 per cent of deaths are due to these conditions, as against only 2 per cent of the sicknesses. In other words, these diseases manifest themselves relatively rarely in definite attacks of sickness, although they undoubtedly shorten life and make life much less enjoyable while they last.

The prevalence of "chronic' conditions as ascertained by this study is of interest. Of each 1,000 individuals on the average 34 were affected with arthritis, lumbago and myalgia; 22 with neuralgia, neuritis and sciatica; 21 with diseases of the heart; 10 with chronic indigestion and other intestinal disorders; 10 with appendicitis; and 7 with nephritis.

The further query suggests itself—at what age is the individual least able to withstand diseases after he has been attacked? One way to measure this is to compare the attack, the greatest resistance to death in childhood being the age period 5 to 14. The lowest resistance is in infancy and early childhood, 0 to 4 years, and in middle and old age. Ability to survive illness thus varies markedly from resistance to illnesses at different ages, particularly in childhood, (5 to 14) when the average individual suffers from illnesses frequently, but has a relatively small chance of dying, and in the older years when not only does his susceptibility to illness increase, but also his chance of death. This is due partly, of course, to the

nature of the illness occurring at these ages, and partly to the diminished ability to resist the diseases which manifest themselves in sickness.

It is believed that one of the most important lessons to be drawn from this study is that public health has as yet barely touched the task of preventing the conditions which manifest themselves in physical and mental impairments, in inefficiency and illness, and in postponable death. Plague and pestilences have been diminished, infant and child mortality from infectious and intestinal disorders, and healthful living is being established more and more firmly as a popular ideal, but aside from these the prevention of disease remains as an outstanding problem yet to be solved.

The hope of the future lies in the continued and increasing growth of scientific knowledge which can be applied to the protection against disease, and the promotion of the public health.

Reviews

International Clinics. A Quarterly of Illustrated Lectures and Especially Prepared Original Articles on Treatment, Medicine, Surgery, Neurology, Pediatrics, Obstetrics, Gynecology, Orthopedics, Pathology, Dermatology, Ophthalmology, Otology, Rhinology, Laryngology, Hygiene, and Other Topics of Interest to Students and Practitioners. By Leading Members of the Medical Profession Throughout the World. Edited by HENRY W. CATTELL, A.M., M.D., Philadelphia, Volume I, Thirty-eighth Series, 1928. 307 pages, three colored plates and numerous figures. J. B. Lippincott Company, Philadelphia and London, 1928. Price in cloth, $3.75.

The contributors to this volume comprise L. F. Barker, Herbert A. Black, H. W. Cattell, F. J. Cleminson, Ralph Colp, George G. Davis, John B. Deaver, Leonard S. Dudgeon, J. Epstein, Harold Ernberg, J. H. Garberson, P. N. Hansen, W. F. Harriman, C. W. Henney, E. L. Jones, E. S. Judd, K. H Krabbe, P. Noubecourt, F. Norsk, W. J. O'Donovan, J. R. Oliver, H. J. Panner, C. V. Patrick, John Phillips, W. D. Reid, Georg Schaltenberg, Victor Schmieden, James Strandberg, Alb. Tillisch, A. Westergren and A. Whittaker. Under Diagnosis and Treatment there are nine articles, dealing respectively with Visceroptosis, Light Treatment, Vertebra Plana, Sanochrysin, Tularemia, Syphilis, Red Cell Sedimentation Reaction, Human Motility, and Polymucositis. Under Medicine there are three articles: Coincident Intestinal Amebiasis and Syphilis, Chronic Epidemic Encephalitis and Bacterial Heart Disease. Under Pediatrics there are two papers, one on the Clinical Teaching of Pediatrics at Paris, and the other on the Sachska Children's Hospital at Stockholm. In the section on surgery the following subjects are discussed: Uterine Fibroids, Operations and Demonstrations at the Chirurgische Universitäts Klinik in Frankfurt-am-Main, Surgical Demonstrations at the Kommune hospital of Copenhagen, Otogenous Cerebral Abscess, and Surgical Treatment of Goiter. Under Traumatic Surgery there are presented: Ball Splint for Hand Fractures, Fractures of the Long Bones and Use of Pedicle Grafts in Traumatic Surgery. Two articles are given to Otolaryngology: Tonsillectomy by Use of an Electrically Lighted Mouth Gag and The Otolaryngological Clinic of the Middlesex Hospital. The single paper under Ophthalmology deals with Disturbances of the Autonomic Nervous System by Eye Stress. Under Pathology one article describes specimens of Fetus Papyraceus, Premature Separation of Placenta and Rupture of Uterus. The other article gives the technique of a New Method for the Rapid Microscopical Diagnosis of Tumors. The 1927 Mütter Lecture of the College of Physicians of Philadelphia by E. S. Judd on The Pathogenesis of Gastric and Duodenal Ulcers follows. Under Medical History J. R. Oliver presents an interesting and readable paper on The Renaissance. A few medical questionnaires come next and the volume closes with a review of the Progress of Medicine During 1927 by the editor, H. W. Cattell. This volume equals in value its predecessors; there are some good and interesting papers presented, while others have no other value than as padding. As in other volumes the articles written by foreigners are very elementary, and some of them hardly worth the printing. Strandberg's article on the Change in the Clinical Picture of Syphilis is an exception and well worth the reading. The surgical articles are on the whole of more practical value than those under the other headings. Reviews of annual progress in medicine are usually unsatisfactory because of inadequate surveys

of the current literature and lack of recourse to original articles. In spite of its defects the present volume contains enough valuable material as to make its perusal worth the while.

First Aid and Medical Service in Industry. A Survey Conducted by DR. H. L. DAIELL. Published by Johnson and Johnson, New Brunswick, N. J. 136 pages, numerous illustrations. Distributed free of cost to any physician interested in first aid and medical service in industry.

The book is a condensation of a special survey of a number of typical industries in the United States. It was made to ascertain the methods employed and the service rendered to employees in the treatment of injuries following the preliminary measures of first aid. The survey included the equipment of first aid rooms, dispensaries and emergency hospitals, inoculation service, physical examination, welfare work, first aid by the layman, etc. Reports of over seventy industries are given, showing those employing from 5,000 to 100,000 operatives, with full detail as to the service, with illustrations of dispensaries, operating and examination rooms. The book also contains specimens of hospital and accident report forms and records of physical examination, with an addenda of miscellaneous contributions. In the reports of specific industries surveyed, only certain types have been selected and only salient points included. The work, it is believed, is the first attempt at such a survey of so important a field. The review has been published at the request of many workers in the field. Much valuable information is contained in this little volume, indispensable to medical men engaged in this line of work.

How to Make the Periodic Health Examination. A Manual of Procedure. By EUGENE LYMAN FISK, M.D., Medical Director, Life Extension Institute; and J. RAMSER CRANFORD, M.D., Assistant Medical Director, Life Extension Institute. Foreword by Major General Merritte W. Ireland, Surgeon General, U. S. Army. 393 pages, 81 figures and charts, bibliography. The MacMillan Company, New York, 1928. Price, $4.00.

This book is dedicated to the memory of Horace Dobell, M.D., (1828-1917) in whose writings sixty-five years ago appeared the first reference in medical literature to the periodic health examination. In his "Lectures on the Germs and Vestiges of Disease and on the Prevention of the Invasion and Fatality of Disease by Periodical Examinations," London, 1861, Dobell said "I wish, then, to propose as the only means by which to reach the evil and to obtain the good, that there should be instituted, as a custom, a system of periodical examination, to which all persons should submit themselves, and to which they should submit their children." The idea urged unsuccessfully by Dobell is now reaching fulfillment. There is a wide-spread and constantly increasing interest in the periodic health examination movement. It is receiving attention, not only from voluntary health organizations, industrial concerns and insurance companies, but also from hospitals, clinics, individual physicians and the public generally. The National Health Council, which includes in its membership such important organizations as the American Public Health Association, the National Tuberculosis Association, and the United Public Health Service, some time ago sent out a nation-wide appeal for a physical examination for everybody at least once a year. The American Medical Association has requested the physicians of the country to equip themselves to render this examination service and the idea is being taken up in earnest by state and county medical bodies. However, the institutions and physicians now specializing in health examinations cannot hope to accomplish the task before them without the aid of reinforcements. It is evident that the great bulk of the work must ultimately fall upon the general profession. The physician must be trained to the proper conduct of this specialized type of medical work, and for this training there is need of a practical manual of procedure. In February, 1925, a small manual for this purpose was put out by the authors, with the assistance of a special committee of the medical staff of the Life Extension Insti-

tute. Before that time there was no definite standardized outline of procedure available to physicians conducting periodic health examinations covering in an intensive way each region of the body. For more than two years the original manual has been used by physicians at the head and branch offices of the Institute, and it has furnished the groundwork for this more comprehensive volume. It is hoped that this volume will fill the need for a practical manual of procedure to serve as a guide to the physician in the conduct of this specialized type of medical work. The chief merit of the manual may be said to lie in the fact that it represents the consensus of judgment of physicians dealing with the practical problems involved in the conduct of the periodic health examination service, covering a thirteen-year experience and the examination of more than five hundred thousand lives. In the preparation of the volume reference has been made to the best scientific literature available in checking up the material presented. Introductions to the various sections have been written by George C. Andrews, A. Bassler, Lawrason Brown, Louis Casamajor, C. A. Drake, A. C. Fones, E. L. Keyes, J. M. Lynch, Edward Martin, John McCoy, R. T. McKenzie, J. O. Polak, M. P. Ravenel, S. C. Smith, R. T. Taylor and W. Finne. These aid in giving the physician a true perspective as to the importance in a general physical examination of thorough attention to every region of the body. The general arrangement of the volume is: Introduction; Preliminary Procedure; Regional Examination; Laboratory Methods and Standards; Counselling; Essential Points to Cover in Reporting to Examiner; Appendix and Bibliography. The specimen forms and reports included in the Appendix are presented for their suggestive value to the general practitioner who desires to establish a satisfactory office system and to conduct this type of service on a high plane of efficiency. The material presented in this book is all of it of the greatest value to the general practitioner, and it can be utilized by him in acquiring thorough methods of general and special regional examinations. It would be of great value to the medical student and interne as a guide to the acquiring of good and thorough habits of examination. The volume is well written and well printed. It can be recommended as serving its purpose most excellently.

The Young Man and Medicine. By LEWELLYS F. BARKER, M.D., LL.D., Professor Emeritus of Medicine, Johns Hopkins University. Vocational Series, Edited by E. Hershey Sneath, Ph.D., LL.D., Yale University. 202 pages. The MacMillan Company, New York, 1928. Price in cloth, $2.50.

This is one of the vocational series designed to help young men about to make that most important decision—the choice of one's life-work. In spite of the important issues involved in a man's vocational career, little has been done in a practical or systematic way to help our college young men to a wise decision in such a determination. The struggles of the average college student in his efforts to settle this important question for himself, the perplexities, embarrassment and apparent helplessness are pathetic. This is largely due to his ignorance of the nature of the professions and other vocations which appeal most strongly to the college man. Consequently, he does not know how to estimate his fitness for them. He cannot advise advantageously with either his father or his instructor, for both of these are familiar only with the one profession each is following. For this reason a series of books dealing with the leading vocations and prepared by men of large ability and experience, capable of giving wise counsel is a desideratum. Such men are competent to explain the nature of the profession and other vocations which they represent, the personal and educational qualifications necessary for a successful pursuit of the same, the advantages and disadvantages, the difficulties and temptations, the opportunities and ideals; thus, in an adequate way, enabling the student to estimate his own fitness for them. They are also able to make valuable suggestions relating to the man's work after he enters upon his vocation. This vocational series will consist of twelve books written by representatives of the following vocations: Law, ministry, teaching, medicine, journalism,

banking, business, mechanical engineering, electrical and civil engineering, farming and government service. Barker has accomplished a very good service in his presentation of the medical vocation. The first chapter discusses thc decision regarding a life career; the second, the services renderable by the medical profession in our social organization; the third, the personal rewards and satisfactions of medical workers, and the appendix is concerned with the educational considerations of medicine. The subject matter is presented in a sane and conservative manner, giving all sides of the medical calling fairly, without sentimentality or exaggeration. Here is no propaganda for medical training, but a dispassionate description of the medical life in its many aspects, perhaps a little too restrained at times to the older physician who reads it, and who is tempted to greater show of enthusiasm about his own profession. Better, however, that the young man's choice should be founded upon a conservative presentation than upon an over-zealous enthusiasm. The book is very readable, the facts are solid, and are logically presented. We particularly recommend it, as we do the entire vocational series, for a prominent place in the shelves of every High School library.

College News Notes

1928-29

BOARD OF GOVERNORS

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The program of the New Orleans Clinical Session of The College seems to be unanimously voted the best and most interesting in the history of the organization. It has been the constant effort of this office, of the Officers and Regents and of the General Chairman to benefit by each year's experience in improving each succeeding Session, and we shall appreciate your comments and suggestions for further improvement.

The next meeting place cannot be selected until the next Regents' Meeting in May or June. Meantime, we should appreciate an expression from you as to your preference for the next meeting place. The following places have been suggested: Rochester, Minn.; Baltimore, Md.; Philadelphia, Pa.; Minneapolis-St. Paul, Minn.; Montreal, Que. Other suggestions may also be made.

By direction of the President, the spring meeting of the Board of Regents of The College will be held in Washington on April 29, 2:00 P.M., prior to the meeting of the Association of American Physicians. The meeting will be held in the District of Columbia Medical Society Building, 1718 M Street. (Please note the address and the hour.)

Among matters to be considered at that time are: Reports of the new Committee on Standards of Admission, Committee on Credentials, and the Finance Committee. The personnel of these new Committees, appointed in accordance with the Minutes of the last Regents' Meeting at New Orleans, are given above.

POST-CLINICAL CRUISE OF THE COLLEGE

The New Orleans Clinical Session in addition to being one of the most successful and profitable meetings ever held, especially in the field of tropical and semi-tropical medicine, was also a very fitting introduction to the Caribbean Cruise, March 10 to 27, to Havana, Cristobal, Colon, Canal Zone, Panama and Spanish Honduras. In fact some of the leading speakers on the New Orleans program, Dr. Aristides Agramonte of Havana, and Dr. William James of Panama, accompanied the party on their southward trip and provided further instruction and entertainment both en route and in their home communities. This afforded an insight into local conditions otherwise unobtainable, and proved once more the medical profession as the greatest fraternity in the world.

The personnel of the party was headed by both the retiring president, Dr. Frank Smithies of Chicago, and the present president, Dr. Charles F. Martin of Montreal, and the executive secretary of the College, Mr. E. R. Loveland of Philadelphia. Other physicians with members of families and friends comprised a party of about forty. The commodious S. S. Cartago of the Great White Fleet (United Fruit Company) was our pleasant and hospitable home throughout the trip, except for one night at the Hotel Tivoli in Panama.

Havana was the first stop. A bright clear morning sun illumined the beautiful harbor, the historic Morro Castle, the Maine monument and the colorful Prado and Ocean drive of the newer section of the City. Dr. Rainold was making his first return thirty years after his service in the medical corps of the Army during the Spanish American War, when he witnessed the surrender of General Weyler and the beginnings of sanitation under Gen. Leonard Wood. The contrast today in general cleanliness and healthfulness was most striking. A general sightseeing tour of the city covered such things as the beautiful University of Havana, the cathedral which once housed the remains of Christopher Columbus, the headquarters of the Cuban Congress and President's palace, Morro Castle with its epitome of three hundred years of Spanish military rule, but now quite unfortified, a typical tobacco factory, the shopping districts, the beautiful American suburbs, private clubs and the most distinctive Casino with its Monte Carlo atmosphere.

Dr. Aristides Agramonte, now the highly respected professor of bacteriology in the University of Havana, at one time was the Minister of Health in the so-called "honest cabinet" of the former President of Cuba. Dr. Agramonte entertained generously in his own home and elsewhere during the stay in Havana. At the ship on leaving he introduced relatives and friends in a diplomatic group from Colombia and Ecuador. A party was given in his honor the following night on shipboard where felicitations were extended to him by oratory and radio.

Mr. Yepes of Bogota, Colombia, legal attaché to the foreign office and member of the Colombian delegation just returning from the Pan-American Conference, was able to give those interested, first hand information about that important international meeting, especially as to the universal South American feeling against intervention by the United States.

Cristobal and Colon, Canal Zone, were reached after three days of sailing in perfect weather. After shopping tours and the unfailing hospitality of Dr. James at the Strangers' Club, the westward transit of the Isthmus was begun. Three relays were made. The first was by auto to the famous Gatun locks which in three stages lift ships to the level of Gatun Lake, eighty-five feet above sea level. The Gatun dam, including spillways, is 8,400 feet long, and backs up the Chagres River maintaining the lake level and providing the water supply for the operation of the locks. The second relay was by steamer across Gatun Lake and through the famous Culebra Cut section of the canal amidst fascinating tropical scenery and vegetable and animal life. The remainder of the trip from Pedro Miguel lock to Panama was completed by auto through delightful driveways abounding with flowers, fruits and birds. Tivoli Hotel was headquarters for the Panama stay. The City

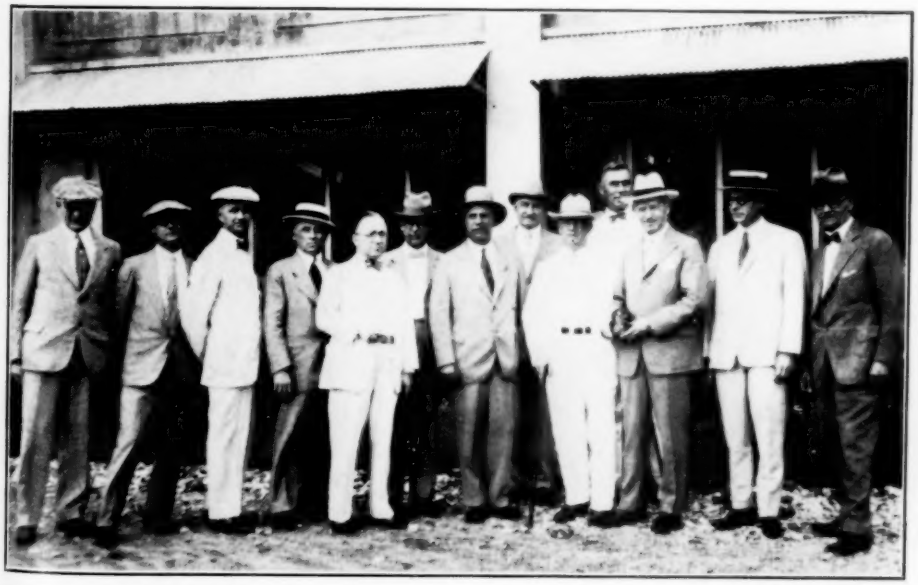
has a population of about 60,000, the old section having the same narrow streets and quaint architecture seen in Havana. A sightseeing trip was made, ending at the site of old Panama and the ruined tower, destroyed by the buccaneer, Henry Morgan, over three hundred years ago. Cocoanuts, cashew nuts, papaya, plantain, mangoes and many other tropical fruits were seen en route.

In the evening an elaborate dinner dance was given at the Union Club by members of the local medical profession, especially Dr. James, Dr. Briscoe, Dr. Reader, Dr. Avery and their associates. This was a most delightful party in an open air pavilion on the shore of the Pacific Ocean. Representative people from the city and the staff of the Ancon Hospital were present, including Dr. Paredes, an alumnus of the University of Pennsylvania, son-in-law of the President of the Republic of Panama and Minister of Health co-operating with the United States authorities in the Canal Zone.

Monday, March 19, was marked by a visit to the famous Ancon Hospital. A special demonstration of tropical diseases was given by Dr. Bates, Director of Laboratories, and others. The colon of a fatal case of amebic dysentery was shown, illustrating the enormous thickening of the bowel in severe cases, sometimes simulating carcinoma. Various phases of malaria, including the structure of the different species of mosquitoes, a malaria-like infection of cattle, trypanosomiasis of horses, leprosy, pellagra and a collection of venomous snakes were among the things presented. The hospital is equipped with all modern facilities in X-ray, electrocardiographic and other apparatus, and is a monument to American medicine. Supt. Eklunzer and the medical staff were very cordial in their attentions to the visiting physicians. One can justly feel proud of being an American on visiting the Canal Zone and seeing the efficiency of sanitation and general administration. The return trip to Colon was made by rail. Large banana plantations and quaint native huts were seen among the mountains.

On leaving Panama, the party presented Dr. James with a Dunhill pipe and Mrs. James with a silver flower basket as an expression of appreciation of their fine spirit of hospitality.

Puerto Castilla, Spanish Honduras, was the next stop. The harbor is protected on one side by a small range of mountains



PART OF GROUP VISITING HOSPITAL AT CASTILLA, HONDURAS

5,000 feet high. An eighteen-mile railroad trip was made to the village of Truxillo, one of the oldest settlements in the new world. It gave a good idea of an inland town, the Honduranian life, the native Carib village and the surrounding country. It was very obvious that development by outside capital such as the United Fruit Company was a blessing to the whole district. The Fruit Company maintains a banana plantation there with a payroll of about 6,600 employees. There is a complete commissary establishment, a club house and an excellent hospital. At the latter, ward rounds were enjoyed through the courtesy of Dr. Phelps, Superintendent, and his associates. Malaria is their main problem. Most patients have it, either alone or complicating other conditions such as pneumonia, which often runs a long unresolved course. They believe they get good results in these cases with 20 c. c. of 1% mercurochrome intravenously. They are using 1% tartar emetic in both leishmaniasis and chancroidal infection. Ninety per cent of their cases have hook worm infestation, which is treated with oil of chenopodium and carbon tetrachloride incidental to their treatment for other conditions. Amebiasis is a less important disease at present in Castilla. Tuberculosis occurs and runs an unfavorable course. The natives stand disease, even measles, very poorly, but recover surprisingly well from extensive injuries.

After a pleasant evening's entertainment at the club house, and witnessing the loading of 65,000 bunches of bananas on board the Cartago, the party said goodbye to Honduras.

Two days more of perfect weather and Havana was revisited for a short hour or two. Some of the party stayed over to return by way of Florida. The rest, after a few words with Dr. Agramonte who came aboard to greet the party again, and after a few hasty purchases, continued the fair weather sailing to New Orleans. During the Cruise, the party was entertained by deck games, special dinners and other social functions. The whole tour was so satisfactory that it was suggested that some similar trip be made an annual affair following the Clinical Sessions. Many close friendships will be formed within the College of Physicians, between members in widely separated parts of the country and opportunities for instruction and recreation will be provided under the most pleasant circumstances.

V. C. Rowland, F.A.C.P.

Cleveland, Ohio